The epidemiology and treatment of infantile spasms

Lux, Andrew Laurence

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The Epidemiology and Treatment of Infantile Spasms

Andrew Laurence Lux

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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Abstract

This thesis examines several aspects of the debate on the choice of best first-line treatment for infantile spasms. The first part of the thesis describes, analyses and interprets outcomes from the *United Kingdom Infantile Spasms Study (UKISS)*, a multicentre randomised controlled trial that compares treatment with prednisolone or tetracosactide (hormonal treatments) against vigabatrin. This study was coordinated from the Bath Unit for Research in Paediatrics at the Royal United Hospital, Bath, and showed that the early primary clinical response, *cessation of spasms*, was significantly more likely in infants who were allocated hormonal treatments. However, the overall proportions with relapse-free response at the end of the study period, when the child reached the age of 12 to 14 months, were similar in all three treatment groups. In a group of infants of *a priori* interest who had no identified underlying aetiology, neurodevelopmental outcomes were significantly better in children who had been allocated hormonal treatments, although this finding was not robust within a sensitivity analysis.

The second part of the thesis examines problems with case definitions and outcome measures in epidemiological and interventional studies of infantile spasms, and describes the development of *West Delphi*, a consensus elicitation process that has produced published proposals for standardised case definitions and outcome measures for such studies. Its most novel proposals were: (1) that the primary clinical outcome *cessation of spasms* should be defined by the absence of observed spasms for at least 28 days from the time of the last observed spasms, with the last spasms being observed within 14 days of treatment allocation; and (2) that there should be a standardised primary electroclinical response that studies should also report as a primary outcome.

Declaration

I declare that the work presented in this Ph.D. thesis consists of my original work. It was performed with help from investigators participating in the United Kingdom Infantile Spasms Study, and with help from contributors to the West Delphi Group. Lists of contributors appear in appendix A. Details of contributions to the United Kingdom Infantile Spasms Study are stated in chapter 2, and in particular section 2.1.1; and contributions to the West Delphi consensus statement are stated in chapter 5. The initial study design for the United Kingdom Infantile Spasms Study was formulated before I joined the study team, but I contributed to the design of instruments for data collection, including the UKISS trial folders and patients' diaries; and I designed and constructed the initial UKISS study electronic database. Work relating to the submission of applications for ethical and management approval was shared primarily with Dr Stuart W. Edwards, as was work relating to data collection and recording. The *BMJ* paper on response times of ethics committees was my original idea, and I was jointly responsible for the study design with Prof. John P. Osborne and Dr Edwards. The drafting of the *Lancet* and *Lancet Neurology* papers was shared with Prof. Osborne and other members of the UKISS trial steering committee, and data analysis was performed by me and Dr Anthony L. Johnson, who was the official statistician to the study. The idea behind the West Delphi consensus status was originally suggested by me and took shape in discussions with Prof. Osborne. Members of the West Delphi Group were jointly responsible for the consensus statement that appeared in *Epilepsia*. I acted as facilitator and drafted the paper for publication, incorporating and seeking consensus on any amendments.

Acknowledgements

I wish to express my gratitude to Professor John P. Osborne, my supervisor in this project, chair of the *United Kingdom Infantile Spasms Study*, and co-guarantor of *West Delphi*, without whom this thesis would not have been conceived, and whose support and encouragement have been constant. I wish to thank Dr Stuart W. Edwards, Research Fellow at the Bath Unit for Research in Paediatrics, and the UKISS Study Administrator, for his diligent and systematic approach to ensuring that UKISS was successful. Further thanks are due to Dr Finbar J.K. O'Callaghan, a third member of the UKISS steering committee whose advice I value greatly. I wish to thank Mrs Karen Giles, whose keen skills in information technology have been of great benefit to the study. Further thanks are due to Mrs Heather Hill, who provided proficient technical support, especially in the administration of West Delphi.

The studies reported here required the participation of several hundred paediatricians and paediatric neurologists – throughout the UK in the 150 centres that were eligible to enroll participants for UKISS, and internationally in the 15 countries participating in West Delphi. The names of these doctors, who gave generously of their time and enthusiasm, appear in appendix A. Particular thanks are due to the members of the UKISS steering committee and the data monitoring and ethics committee, and especially to Dr Ellie Hancock, whose steadfast work during the early part of the study laid extremely strong foundations for what followed. Special thanks are also due to Dr Tony Johnson, the study statistician, who performed several of the analyses presented in the thesis.

Funding for part of these studies was generously provided by the Bath Unit for Research in Paediatrics (BURP) and by Cow & Gate Limited. I also acknowledge a travel grant kindly given by Hoechst Marion Roussel.

I could not have completed this work without learning about biostatistics, child neurology, and clinical neurophysiology, and I would like to thank the members of institutions in Bristol, London, and St. Louis that have inspired and guided me in these areas. My formal training in epidemiology and biostatistics was from Professor Stuart J. Pocock and other members of the Medical Statistics Unit in the Department of Epidemiology and Population Health at the London School of Hygiene & Tropical Medicine. My training in child neurology and clinical epilepsy was provided by Professor P.M. "Mick" Leary and Drs Philip E. Jardine, Jayesh S. Patel, and Peta M. Sharples in the Department of Paediatric Neurology at Bristol Royal Hospital for Children and at Frenchay Hospital, Bristol. And I learned clinical neurophysiology and paediatric epilepsy from Drs Susan T. Arnold, W. Edwin Dodson, Kevin Ess, Frank Gilliam, Christina Gurnett, K. Liu Lin Thio, N. Edwin Trevathan, Michael Wong, Kelvin Yamada, and John M. Zempel at Washington University School of Medicine; and with help from Barb Smith and the EEG Laboratory Staff at St. Louis Children's Hospital, St. Louis, Missouri, USA.

In the course of this research, I have had the great privilege of meeting the inspirational paediatric neurologist, Professor Yukio Fukuyama of Tokyo Women's Medical University. He was publishing in this research area when I was myself an infant. I am very grateful to him for his interest in this current work and for his generous support.

Finally, the main cost of undertaking such a product is paid in time that should have been spent with my family doing things that are properly considered more exciting. I appreciate the support and encouragement of my wife, Prisca, and the welcome distractions provided by Eric and Emma; and I hope that they will consider this to have been a worthwhile project.

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Chapter 1

Introduction

1.1 Historical background

The first written description of what is now known as infantile spasms appeared in 1841 [1]. William James West, a general practitioner in Tonbridge, Kent described, in a letter to the *Lancet*, episodes of repeated head nodding in his son, James Edwin West [2, 3]. A contemporary of West, William Newnham, had seen a case a year earlier. After reading West's account, Newnham compiled details of four cases, including the one that he had treated and that of James Edwin West [4].

Little therapeutic progress occurred during the century after West's description, though the names by which the disorder was known proliferated [5]. However, there was a breakthrough in the early 1950s, with published reports of the disorder being associated with characteristic EEG findings. In 1949, Vasquez and Turner described ten cases to the *Sociedad Argentina de Pediatría*, with electroencephalographic findings in eight cases that they described as a diffuse, paroxysmal cerebral dysrhythmia* that was of high voltage, diffusely disorganised, and irregular† [6].

*"...*una difusa disritmia cerebral paroxística...*"

†"...*de gran voltaje, difusamente desorganizada e irregular...*"

In 1952, Gastaut and Rémond described what appears to be the same condition, distinguishing a form of bilateral myoclonus that they called *myoclonies type B*. They described an ictal spike-and-slow-wave complex[‡] that tended to repeat in a more or less periodic fashion[§] [7]. And that same year, Gibbs and Gibbs provided an influential description in English in their *Atlas of Electroencephalography* [8]:

> ... random high voltage slow waves and spikes. These spikes vary from moment to moment, both in duration and location. At times they appear to be focal, and a few seconds later they seem to originate from multiple foci. Occasionally, the spike discharge becomes generalized, but it never appears as a rhythmically repetitive and highly organized pattern that could be confused with a discharge of the petit mal variant type. The abnormality is almost continuous.

Gibbs and Gibbs called the characteristic EEG pattern *hypsarrhythmia*, a term derived from the Greek $\chi\upsilon\psi\varepsilon\lambda\circ\varsigma$ (high) and $\alpha\rho\rho\iota\vartheta\mu\circ\varsigma$ (non-rhythmic) [9].

In the late 1950s, investigators used this new clinical and electroencephalographic information to study the effects of potential treatments. There were soon reports from Belgium [10], France [11], Japan [12], Switzerland [13], and the United States [14, 15] on the treatment effects of adrenocorticotrophic hormone (ACTH) and corticosteroids. These became the mainstays of treatment for the condition that became known best as *infantile spasms* or *West syndrome*.

Although several new antiepileptic drugs became available during the next three decades, none was more effective than hormonal treatments. However, vigabatrin, which was first licensed for therapeutic use in 1989, proved to be an effective treatment of infantile spasms and came to be considered as a valid alternative first-line treatment for infantile spasms. One small randomised trial

[‡] "... *le complexe* « pointe-onde lent »..."

[§] "... *tendent parfois à se répéter, de façon plus ou moins périodique...*"

suggested that it is a particularly good treatment for infantile spasms when the underlying cause is tuberous sclerosis (TSC) [16]. Since it is administered orally and it was believed to have only minor adverse effects, vigabatrin became a popular choice as first-line treatment of infantile spasms.

1.2 Content and scope of this thesis

This thesis examines the relative effectiveness and safety of hormonal and vigabatrin treatment of infantile spasms, and reports the results of a multicentre randomised trial. This introduction discusses definitions, classification and clinical features of infantile spasms. It summarises the basic epidemiological features, the frequency and underlying disorders associated with infantile spasms. And it discusses previous studies of treatments for infantile spasms with a particular focus on randomised trials that include hormonal treatments or vigabatrin.

Chapter 2 outlines the design of the *United Kingdom Infantile Spasms Study (UKISS)*. It describes how the study protocol was developed after initial approval was granted; some aspects of the administration of the study; and issues relating to safety, licensing, and ethics. Chapter 3 reports early outcomes from the UKISS randomised trial, involving the period up to study day 14; and chapter 4 reports outcomes from the later part of the study, including relapse of spasms in primary clinical responders, progression to other seizures types, and neurodevelopmental outcomes.

Chapter 5 reports the administration and results of *West Delphi*, a consensus elicitation process that I developed with Professor John Osborne in response to problems that became apparent when we critically appraised the design of UKISS and other studies of infantile spasms.

Chapter 6 discusses, in the context of earlier and recent research, the find-

ings of UKISS and the results of West Delphi, and how these two initiatives might influence future investigations and the treatment of infantile spasms.

1.3 General reviews of infantile spasms

This thesis cites many important published articles in the field of infantile spasms, particularly those relating to case definition and treatment. To get a general overview of infantile spasms, good resources are the reviews given in the short monographs by Jeavons and Bower [17], and by Lacy and Penry [18]; and collected information in the books edited by Gastaut, Roger, Soulayrol and Pinsard [19], Dulac, Chugani and Dalla Bernardina [20] and by Schwartzkroin and Rho [21]. The proceedings of a 1985 symposium on infantile spasms is published in volume 9 of *Brain & Development* [22]. Recent reviews that appear as chapters in major textbooks of epilepsy include those by Dulac, Plouin and Schlumberger [23] and that by Holmes and Vigevano [24].

1.4 Definition of infantile spasms

The term *infantile spasms* was not established as the standard term for this epilepsy condition until the early 1960s. Gastaut and Poirier, in their report of a symposium held in Marseilles in 1960, listed fifty-five synonyms for this disorder: 21 English; 9 German; and 25 French or latinate in origin [5]. Many of the names describe the nature of the movement: for example, *jackknife convulsions*; *Komplimentierkrämpfe*; and *spasmes salutoires*. Other names suggest the suddenness or severity of the movements: for example, *lightning major seizures*; *Blitz-Nick-und-Salaamkrämpfe*; and *propulsions epileptiques*. A further synonym, *l'encéphalopathie myoclonique infantile avec hypsarrhythmie (EMIH)* (infantile myoclonique epilepsy with hypsarrhythmia), was coined as a result of the Mar-

seilles symposium, but this term has not stood the test of time.

In tribute to the doctor who gave the first written description of the disorder, Gastaut and others attending the symposium suggested the term *West syndrome*, at that time recommending that this term be used to describe historical aspects of the disorder [5]. Since then, however, the term *West syndrome* has been used in wider and inconsistent contexts, sometimes referring to the triad of spasms, hypsarrhythmia, and developmental delay [18]; sometimes referring to the former two features without requiring the third [25]; and at other times referring to any two of the three features. For many physicians, the term *West syndrome* is simply a synonym for infantile spasms [26].

The term *infantile spasms* ("Spasms, Infantile") was introduced as a Medical Subject Heading (MeSH) term at the (United States) National Library of Medicine in 1977 [27]. It gives the definition: "An epileptic syndrome characterized by the triad of infantile spasms, hypsarrhythmia, and arrest of psychomotor development at seizure onset." The triad thus defined does require developmental delay from the time of onset of spasms. The MeSH definition distinguishes two forms: *symptomatic* and *cryptogenic*, with the latter term being considered to be synonymous with the term *idiopathic*.

Other terms, *epileptic spasms* and, more simply, *spasms*, have been used to describe this seizure type occurring in clusters [28]. These terms disregard any limits of age and include the so-called *periodic spasms* that were first described by Gobbi *et al* [29]. It has been suggested that the term *epileptic spasms* may become preferred to *infantile spasms* [28].

Periodic spasms are clusters of spasms that occur in older childhood, and which do not have an EEG pattern of hypsarrhythmia. They often start with a focal seizure or EEG discharge followed by spasms that are often asymmetric or even unilateral. The EEG then typically shows slow waves time-locked to the clinical spasms, with superimposed low-amplitude fast activity.

There is substantial disagreement about the classification and definition of infantile spasms in three areas. First, which features are necessary and which sufficient to define the infantile spasms. Second, how infantile spasms should be divided into the aetiological categories that are variously described as symptomatic, idiopathic, and cryptogenic. And third, which spectrum of epileptic disorders infantile spasms falls within, and how to distinguish infantile spasms from other members of such spectra.

1.4.1 Necessary and sufficient features

There is no consensus on what constitute necessary and sufficient features to define infantile spasms. Most investigators would agree that spasms involving axial muscles and an associated abnormal EEG would be necessary features, but some investigators have suggested that relatively subtle movements associated with a hypsarrhythmic EEG are sufficient to define a case. Thus, even axial spasms are not considered by all investigators to be a necessary feature. Some investigators have suggested that features such as non-focal onset, onset before one year of age, the occurrence of spasms in temporal clusters, and left-right symmetry of spasms are necessary features.

It is recognised that a hypsarrhythmic EEG pattern can occur in the absence of spasms, and so this cannot be considered to be a sufficient feature. Neither is hypsarrhythmia a necessary feature, since it is known that other EEG patterns are found early and late in the evolution of infantile spasms, and that any EEG pattern may be modified by treatment. Despite this, the term *hypsarrhythmia* was used during the 1950s and 1960s as a synonym for infantile spasms, and hypsarrhythmia may well have been portrayed by some investigators as being both a necessary and sufficient condition for the diagnosis of infantile spasms [30].

The range of ideas and disagreement about what are necessary and suffi-

cient features of infantile spasms are illustrated by published reports of commissions and workshops sponsored by the International League Against Epilepsy (ILAE). The ILAE International Classification of Epileptic Seizures of 1970, inspired by Gastaut, recommended that infantile spasms be classified as a type of generalised seizure [31, 32]. This classification implies bilateral symmetry and a non-focal onset. The classification also stated that infantile spasms: (1) is a seizure disorder of infants; (2) has an underlying substrate and cause that is unknown; (3) is associated with an interictal EEG that shows hypsarrhythmia; and (4) shows varied ictal EEG changes: usually flattening, but sometimes more prominent spikes and slow waves.

A proposal for revised clinical and electroencephalographic classification of epileptic seizures in 1981 did not mention infantile spasms [33], but a proposal for classification of epilepsies and epileptic syndromes published in 1985 did include infantile spasms and stated that its onset had to occur within the first year of life [34]. A further proposed revision of this classification of epilepsies and epileptic syndromes, published in 1989, based its definition of infantile spasms on the triad of spasms, hypsarrhythmia, and developmental delay, but conceded that one element of the three may be missing [35]. It required that onset, "always occurs before the age of one year," and added that the age of onset peaks between 4 and 7 months of age. The proposal added further epidemiological and therapeutic observations, suggesting that the mixed form of spasms is commonest, and that adrenocorticotropic hormone or corticosteroid treatments influence neurodevelopmental outcome.

This 1989 ILAE proposal defined and distinguished symptomatic and cryptogenic infantile spasms. Children would be classified as having symptomatic infantile spasms if they had neurological, developmental, or radiological signs of brain damage preceding the onset of spasms; if they had a known underlying cause; or if there were preceding seizures of another type. Children with-

out these features, which it suggested is a smaller group, would be classified as having cryptogenic infantile spasms.

The Commission on Pediatric Epilepsy of the ILAE held a workshop on infantile spasms in 1991 [28]. This workshop recommended that infantile spasms should not be confined to the International Classification of Epileptic Syndromes, but should be included also in the broader International Classification of Epileptic Seizures. The definition of infantile spasms that was recommended by this commission is generally more permissive than earlier definitions, and is markedly different from that of the 1989 commission. In particular: (1) onset is not confined to the first year of life; (2) the spasms are often associated with hypsarrhythmia during infancy, but this is modified by age, underlying brain lesions, and sleep-wake state; and (3) the definition of West syndrome is determined by the association of the spasms with hypsarrhythmia. The workshop recognised that West syndrome is often associated with developmental delay, but suggested that developmental delay ought not to be required to make a diagnosis of West syndrome.

The workshop made three other important recommendations. First, that the term *infantile spasms* be dropped in favour of the term *spasms*. Second, that the term *modified hypsarrhythmia* should be discarded in favour of describing the specific modifying features in each case. And third, that the term *idiopathic infantile spasms* be reserved for cases with more specific features.

1.4.2 Aetiological subgroups: *symptomatic, cryptogenic,* and *idiopathic*

The terms *symptomatic, cryptogenic* and *idiopathic* have been used in different senses by different investigators. In general, the term symptomatic has been used to describe a child who has a known cause for the infantile spasms.

This cause may be: (1) described in the medical history, as with neonatal encephalopathy with seizures; (2) anatomical, such as a major brain malformation proven by neuroimaging; (3) biochemical, such as phenylketonuria; or (4) a genetic syndrome, such as tuberous sclerosis. However, the term *symptomatic* is often used in cases where no specific underlying aetiology is identified but where it is inferred, probably because there is substantial developmental delay, that a significant underlying aetiology must be present. Dulac and Plouin listed eight definitions of non-symptomatic infantile spasms that have been used by other authors, five of which required there to be normal development before onset of spasms [36].

The terms *cryptogenic* and *idiopathic* have tended to be used as synonyms for any non-symptomatic case. However, these terms have etymologies that suggest a distinction. The term *cryptogenic*, from the Greek $\kappa\rho\upsilon\pi\tau o\varsigma$ (hidden) and $\gamma\varepsilon\nu o\varsigma$ (origin), suggests that an underlying cause is suspected but cannot be found. The term *idiopathic*, from the Greek $\iota\delta\iota o\varsigma$ (self) and $\pi\alpha\vartheta o\varsigma$ (disease), suggests a disorder produced by itself and with no underlying cause.

The 1991 workshop on infantile spasms made use of this distinction to describe the clinical and electrophysiological features of a group of children whom they define as having idiopathic infantile spasms. It suggested that this idiopathic form is distinguished by the following features: (1) normal development before the onset of spasms; (2) no preceding seizures of any type; (3) normal clinical examination (4) normal computed tomography (CT) and magnetic resonance (MR) imaging; (5) hypsarrhythmia occurring between spasms within a cluster of spasms; and (6) no evidence of a focal lesion on either ictal or interictal EEG.

One problem with this definition of an idiopathic group as suggested by Dulac *et al* is that it requires, as part of its definition, normal final developmental outcome [36]. It thus includes information that is not known at the time of

diagnosis and can only be determined retrospectively. Also, the final developmental status might be influenced by factors that are entirely unrelated to and independent of the infantile spasms. The electroencephalographic features of this group, hypsarrhythmia recurring between spasms within a cluster, are not specific to idiopathic cases but are also found in infants with Down syndrome [37].

1.4.3 Associated conditions and distinguishing features

Infantile spasms may also be defined by their relationships to other forms of epilepsy. On the basis of EEG features, Lennox and Davis considered infantile spasms to be related to generalised absence epilepsy, including it as a member of a *petit mal quadrette* [42]. Livingston *et al* suggested that infantile spasms was part of a group of conditions called *minor motor epilepsy* and which included akinetic seizures and head nodding episodes [43]. Gastaut considered infantile spasms to be related to myoclonic epilepsy, hence referring to it as one of the *myoclonies B* [7].

Ohtahara has suggested that infantile spasms are part of a spectrum of age-dependent epileptic encephalopathies consisting of early infantile epileptic encephalopathy (EIEE; Ohtahara syndrome), infantile spasms (West syndrome), and Lennox-Gastaut syndrome [44, 45, 46]. This idea is based on the observation that the clinical and EEG patterns occur at certain ages and during critical stages of development. Features common to the age-dependent epileptic encephalopathies include characteristic EEG features, heterogenous underlying disorders, frequent developmental delay or learning disability, and often intractability to treatment [44].

Many children progress from Ohtahara syndrome to West syndrome or infantile spasms, or from infantile spasms to Lennox-Gastaut syndrome, or both. In a series of children with age-dependent encephalopathies described

by Ohtahara, 9/14 children who had Ohtahara syndrome developed infantile spasms, and 17/88 children with infantile spasms developed Lennox-Gastaut syndrome. Some children progress through all three conditions. This concept of age-dependent epileptic encephalopathies is currently popular.

Aicardi and Chevrie proposed a classification that distinguishes infantile spasms, which would always have a hypsarrhythmic EEG pattern, from myoclonic epilepsies of childhood, which would have spike-wave or polyspike-wave EEG abnormalities without evidence of the more chaotic hypsarrhythmia [30]. Myoclonic episodes tend to be shorter than the episodes associated with infantile spasms, and the duration of muscle contraction associated with each episode can be measured by electromyography (EMG). Tonic seizures tend to last longer than the spasm movements associated with infantile spasms. However, it is arguable whether infantile spasms can be reliably distinguished from myoclonic epilepsies of childhood by episode duration. Some authors have described *lightning spasms*, a form of infantile spasms with spasms of shorter duration. However, they have not justified this classification as a separate form by suggesting features that would otherwise distinguish these cases from other cases of infantile spasms [17, 47].

Ohtahara syndrome consists of tonic spasms occurring during the first few weeks of life associated with an EEG showing a burst-suppression pattern during both wakefulness and sleep. It is often associated with structural lesions, severe neurodevelopmental delay, and progression to other seizure types in later life. Some investigators suggest that Ohtahara syndrome is an early form of infantile spasms [48]. In the same age group, a burst-suppression EEG pattern with erratic myoclonus but no evidence of tonic seizures is consistent with the diagnosis of early myoclonic encephalopathy, which is more frequently associated metabolic disorders. There is continued debate about whether these syndromes are reliably distinguishable [49, 50].

Lennox-Gastaut syndrome usually has an onset between the ages of 1 and 7 years, but so-called early-onset cases may occur during the first year of life [48]. It may be difficult to distinguish early-onset cases of Lennox-Gastaut syndrome from later-onset cases of infantile spasms, particularly since cases of infantile spasms with late onset and cases of Lennox-Gastaut syndrome with early onset less often show typical EEG changes. The diagnosis of Lennox-Gastaut syndrome is considered to be clear once atonic and absence seizures become evident, but it may be impossible to decide whether the earlier features were due to Lennox-Gastaut syndrome or infantile spasms.

1.5 Clinical features of infantile spasms

The clinical features of infantile spasms are described excellently in the monograph by Lacy and Penry [18], and information in this section is taken from that source unless stated otherwise.

There is a general consensus that infantile spasms is a type of seizure disorder, and there is agreement about its fundamental forms. However, there is disagreement about whether subtler movements should be regarded as being infantile spasms. The spasms may be flexor, extensor, or mixed; and the most characteristic movement is a sudden onset of contraction of the muscles involved, this usually occurring with bilateral symmetry and synchrony.

Flexor spasms involve sudden, simultaneous flexion of the neck and trunk; bilateral, symmetrical flexion, abduction, or adduction of the upper limbs; and flexion and adduction of the lower limbs. At the end of a spasm, the upper limbs may be either strongly abducted, resembling a Moro reflex, or adducted across the child's front and resembling a self-embrace. *Extensor spasms* involve sudden extension of the neck and trunk; bilateral, symmetrical extension and abduction of the upper limbs; and extension at the hips and knees. They par-

tially resembles a Moro reflex, and have been described as a *cheerleader spasms*. There can also be *mixed spasms*, which consist of either flexion or extension of the neck and trunk with the limb movements being opposed to the truncal posture. The spasms usually occur in batches or clusters, and the term *mixed spasms* can be used in an alternative sense to indicate that some clusters consist of predominantly flexion movements of limbs and trunk, and other clusters consist predominantly of extension movements. In some children, single spasms occur on some occasions and clusters at other times. Rarely, a child has single spasms on all occasions. Between cases, there are wide ranges in the number of clusters occurring during one day and in the number of spasms occurring within a cluster. As the disorder progresses, there may also be substantial variation in these features within any one case.

1.5.1 Distinct forms of infantile spasms

There is controversy about whether the other forms of infantile spasms described by some investigators are infantile spasms or another type of seizure. One controversial form is the *head nodding* spasm, which seems to precede or remain after the more classical forms of infantile spasms. Some investigators think it is a distinct type of seizure that is associated with infantile spasms, and others suggest that it is a distinct form of infantile spasms.

Another form of spasm that has been regarded as an associated but separate type of seizure by some researchers is the *tonic spasm*. In this form, the child has a rigid posture and a fine tremor of the outstretched limbs. Briefer spasms that resemble myoclonus have been described as *lightning spasms*, as discussed in section 1.4.3.

More arguable forms are those that are described as *partial* or *fragmented* infantile spasms. These include: unilateral spasms; those involving only upper or lower limbs; those involving only part of one set of limbs, such as the

shoulders alone; and those involving flexion of either the neck or the trunk, but not both. Some investigators state that infantile spasms are, by definition, bilateral, symmetrical, and generalised. However, it is generally accepted that some degree of asymmetry and lateralisation, such as turning of the head or rolling of the head to one side, may occur in infantile spasms. In the study of Fusco and Vigevano, asymmetrical spasms occurred only in children with symptomatic infantile spasms, and were noted in 8/20 (40%) of such cases [51]. The cases classified as *symptomatic* in that study included five with "spasms of unknown prenatal etiology."

1.5.2 Other features of spasms

It is difficult to assess whether consciousness is lost during spasms, or merely impaired. The scream or cry that often accompanies the spasms may be a sign of distress associated with spasms, or it may be part of the seizure. Such screams are more likely to occur at the end of a cluster of spasms, rather than before or during the cluster. Other features that may occur during a cluster of spasms include: laughter or smiling; a frightened or confused facial expression; flushing, pallor, cyanosis, or sweating; dilated pupils or fluttering eyelids; staring, rolling or lateral movements of the eyes; nystagmus; the production of tears; hiccups or respiratory arrest; tremulousness; or incontinence of urine or faeces.

Several features have been described during the period between clusters of spasms, the commonest of which are tremulousness, irritability, and rigid posturing, often with arching of the back. These interictal features are thought to be more common in children who suffer more frequent spasms. Drowsiness has been described at the end of a cluster of spasms, and seems to be associated with clusters of longer duration.

1.5.3 Factors that precipitate spasms

Several factors have been described that might, in a predisposed child, trigger spasms. The states of consciousness between sleeping and waking or between waking and sleeping – the so-called *twilight states* – have been described as a triggering factor in many studies. Other putative factors include: handling; feeding; hunger; startle or fright; excitement or anger; urination or defæcation; fever; excessive environmental heat. Twilight states are more likely to occur in the morning and evening, especially in older children. However, no studies have described a tendency for spasms to occur at a particular time of day.

1.5.4 The timing and duration of ictal events

There is no standard definition of the ictal event associated with infantile spasms. Some investigators suggest that a single spasm might constitute an ictal event, but others suggest that the cluster of spasms is the more appropriate measure. Since single spasms can occur, the duration of an ictal event might be as short as a few seconds. Some series have been described in which "several thousands" of spasms have occurred, and an ictal event might last longer than twenty minutes. It seems that spasms are less frequent when they are first noticed, peak in frequency and duration when the disorder is well established, and then diminish in frequency and duration as the disorder resolves.

Fusco and Vigevano reported the mean duration of spasms as recorded by EMG of the deltoid muscle as being 1.25 seconds and 1.56 seconds in cryptogenic and symptomatic groups respectively [51]. The study did not report full ranges or an overall median or mean, but no spasms were longer than 2.4 seconds.

1.5.5 Relationship to other seizures

Antecedent seizures are relatively common. Many children with infantile spasms have had neonatal encephalopathy with seizures. Infantile spasms may be the next seizure disorder to develop, or there may be other seizure types during the interim. Infantile spasms may be preceded by generalised or focal epileptic seizures, the latter especially in infants who have focal neurological lesions. Some investigators have also described myoclonic and akinetic seizures preceding the onset of infantile spasms. Estimates of the proportion of children with infantile spasms who had antecedent seizures are influenced by the classification of seizures such as head nodding, which some investigators regard as being early signs of infantile spasms. Finally, the tonic seizures of early infantile epileptic encephalopathy (Ohtahara syndrome) evolve relatively commonly into infantile spasms.

Concurrent seizures, particulary focal seizures, are common with infantile spasms. Druckman and Chao described concurrent seizures in 26/73 (36%) of children, and Jeavons and Bower described them in 30/112 (27%) of children [17, 52]. Most of these were considered to be generalised seizures, but some were described as focal, akinetic or mixed types. Ohtsuka *et al* have described partial seizures occurring in 40% of children with *West syndrome* [53]. Concurrent partial seizures are recognised to be particularly common in tuberous sclerosis, and EEG-video monitoring has shown that partial seizures can have a complex sequence of close temporal association with the clinical spasms [54, 55]. Plouin *et al* performed EEG-video monitoring on 74 infants and reported partial seizures in half of cases classified as symptomatic and one-third of cases classified as cryptogenic [56]. They reported that this finding was associated with poorer response to treatment with corticosteroids.

Subsequent seizures are also known to be common. Early studies by Jeav-

ons and colleagues showed that about half of the children who became spasm-free developed, either before or after the spasms had ceased, other types of seizure [57, 58]. Subsequent seizures may be generalised, focal, or akinetic, and Lennox-Gastaut syndrome occurs relatively frequently. However, studies have shown substantial variation in the proportion of children with infantile spasms who later develop focal seizures [18].

1.5.6 Differential diagnosis of infantile spasms

The most likely differential diagnoses of infantile spasms are conditions that generally present during the first year of life. They may be divided into two groups: disorders or symptoms that are paroxysmal or episodic and which are not associated with epileptic EEG patterns; and other forms of epileptic seizures or syndromes [48]. Non-epileptic disorders that might be mistaken for infantile spasms include: abdominal pain (colic); benign neonatal sleep myoclonus; benign paroxysmal tonic upward gaze; hyperekplexia; Sandifer syndrome; early breath-holding spells and syncopal episodes; adverse reactions to exogenous agents; paroxysmal dystonia or choreoathetosis; increased Moro reflex with episodes of opisthotonus; episodes of self-gratification or infantile masturbation; and shuddering attacks. Spasms associated with a normal EEG have been termed benign myoclonus of early infancy (BMEI) by Lombroso and Fejerman [59], and benign nonepileptic infantile spasms by Dravet *et al* [60]. BMEI resembles non-symptomatic infantile spasms in several ways. The age at onset is 4 to 9 months, and the spasms occur in series of myoclonic or brief tonic contractions of the neck, shoulders and upper limbs. However, the spasms associated with BMEI rarely occur during sleep; the awake and sleep EEG patterns are normal; and developmental prognosis is normal.

Epilepsy conditions that might be mistakenly diagnosed as infantile spasms include: early myoclonic encephalopathy; early infantile epileptic encephalopa-

thy (Ohtahara syndrome); benign myoclonic epilepsy of infancy; myoclonic-atonic-astatic epilepsies; and early-onset Lennox-Gastaut syndrome. In addition, partial seizures may mimic infantile spasms that are asymmetrical. The differential diagnosis in older children includes Lennox-Gastaut syndrome and periodic spasms [29].

1.6 Electroencephalographic features of infantile spasms

The use of video EEG in the study of infantile spasms was first described by Frost *et al* in 1978 [61]. The system included monitoring of EEG, electromyogram (EMG), electrocardiogram (ECG), electro-oculogram (EOG), respiration rate, galvanic skin responses, and measurement of acceleration of body parts in three axes. These were linked to a synchronous video recording.

1.6.1 Hypsarrhythmia

The classical EEG pattern associated with infantile spasms is hypsarrhythmia, which generally occurs during the interictal period between clusters of spasms. (In some early works, hypsarrhythmia was spelt *hypsarhythmia*, with a single *r*, but Jeavons and Bower standardised the English spelling to have a double *r* in keeping with the Greek rule that a word beginning with the letter ϱ, (*rho*) takes a double ϱ when prefixed [17].) A hypsarrhythmic EEG pattern is neither a necessary nor a sufficient feature of infantile spasms. However, the two are strongly associated, and hypsarrhythmia has been used as a synonym of infantile spasms. One early paper described approximately two-thirds (51/80) of children with hypsarrhythmia as having seizure disorders other than infantile spasms [62].

The classical EEG pattern of hypsarrhythmia described by Gibbs and Gibbs is generally thought to occur in immature and developing nervous systems. The most characteristic feature seems to be that the focal spikes-and-sharp waves are positioned inconstantly, shifting from moment to moment [9]. The pathophysiological mechanism that produces this EEG pattern is not known, but it is likely that it involves both cerebral cortex and subcortex [63]. The hypsarrhythmic pattern may be interrupted by fast waves, high voltage spikes, polyspikes, slow waves, or sudden suppression of electrical activity. The amplitude of the spike-and-sharp waves is often greater over the posterior head regions, a feature that is said to distinguish hypsarrhythmia from the EEG of early-onset Lennox-Gastaut syndrome [9].

Although hypsarrhythmia is generally described as an interictal EEG pattern, it has been said to occur between single spasms within a cluster in the group described as idiopathic by the 1991 ILAE workshop. One early study suggested that hypsarrhythmia can occur at any time between the first few days of life and 3 years of age, but that it most commonly occurs between the ages of 3 and 6 months [15].

Hypsarrhythmia is often present during both wakefulness and sleep, but in some cases it is found only during sleep [17]. In fact, despite the original assertion by Gibbs and Gibbs that hypsarrhythmia is "almost continuous, and in most cases [evident] as clearly in the waking as in the sleeping record," later studies have shown hypsarrhythmmia to be state-dependent and more common in sleep [64].

1.6.2 Atypical and modified hypsarrhythmia

The terms *atypical*, first introduced by Gastaut, and *modified*, first used by Gibbs and Gibbs, are used to describe EEG patterns that are often regarded as being "decidedly abnormal but not truly hypsarrhythmic" [8, 18, 65, 66]. Such EEG

Table 1.1: Features described as *atypical* and *modified* by Gastaut and Hrachovy *et al*, respectively.

Feature	Description	*Atypical*	*Modified*
Amplitude	High amplitude activity	Yes	Yes
Asymmetry	Asymmetry of wave amplitude affecting a part or whole of one cerebral cortex: at its most extreme, hemihypsarrhythmia	Yes	Yes
Attenuation	Episodes of generalised, regional, or localised voltage attenuation, usually lasting from 2 to 10 seconds	No	Yes
Focality	Evidence of spikes and spike-waves associated consistently with an irritative focus	Yes	Yes
Fragmentation	Temporal variation in EEG patterm	Yes	No
Slow wave	Excessive slow wave activity	Yes	Yes
Synchrony	Increased synchronisation between hemispheres, also known as *periodicity*	No	Yes

patterns show a degree of organisation that is described as *synchrony* or *periodicity* and which is said to be distinct from the totally chaotic EEG pattern of *typical* or *classical* hypsarrhythmia.

Gastaut *et al* described five features that defined *hypsarythmies atypiques* (table 1.1) [65]. The first feature was temporal fragmentation during wakefulness, rather than during sleep. They noted that such fragmentation tends to occur prior to resolution of hypsarrhythmia. A second feature was excessive slow wave activity. The third feature contrasted the second: high amplitude fast activity. A fourth feature was an asymmetry of wave amplitude affecting a part or whole of one cerebral cortex. And the fifth feature was spikes and spike-waves associated with an irritative focus.

Hrachovy *et al* also described variations in the EEG pattern, preferring the term *modified* to *atypical*, and noting that rapid eye movement sleep (REM) in particular is associated with marked improvement in the hypsarrhythmic pat-

tern [67]. They suggested that high voltage, asynchrony, seizure type and ictal EEG patterns are features that are maintained. The modifying features they described are: (1) increased interhemispheric synchronisation; (2) asymmetry, at its most extreme, hemihypsarrhythmia; (3) a consistent focus of abnormal discharge; (4) episodes of generalised, regional, or localised voltage attenuation, usually lasting from 2 to 10 seconds; and (5) a pattern that is predominantly high-voltage bilaterally asynchronous slow activity. They described a *periodic appearance* consisting of grouping of spike, sharp wave and slow wave discharges during NREM sleep, and disappearance of hypsarrhythmia during REM sleep. A reduction or disappearance of hypsarrhythmia, lasting for several seconds to minutes and called *relative normalisation*, was noticed during arousal from NREM or REM sleep.

Modifying features included in Gastaut's *atypical hypsarrhythmia* classification: interhemispheric asymmetry, high amplitude slow activity with little sharp wave or spike activity, and signs of a focal irritative lesion. In addition, they described increased interhemispheric synchronisation and episodes of attenuation. Synchrony has also been termed *periodicity*, and has been shown to occur in some cases before the development of typical hypsarrhythmia [63, 68]. It has been suggested that this synchrony is the essential defining feature of *modified hypsarrhythmia* [18].

These features are described in qualitative rather than quantitative terms, and it is likely that there would be substantial inter-rater, and possibly intra-rater variation, in classifications based upon these criteria. Also, the underlying mechanisms that produce these features may have different structural, functional or prognostic significance, and the collective terms *atypical hypsarrhythmia* and *modified hypsarrhythmia* may not be useful. The 1991 ILAE workshop on infantile spasms recommended that these terms are no longer used, and that the specific features are described separately [28]. Hypsarrhythmia

that persists during a cluster of spasms was described by Fusco and Vigevano as a feature that is associated with better prognosis [51]. This has been described by the 1991 Workshop as one of the features that define the idiopathic form of infantile spasms. However, it has also been reported as a feature found in children with infantile spasms and Down syndrome [37].

1.6.3 Ictal EEG features

Fusco and Vigevano described three EEG patterns during clusters of clinical spasms: (1) a medium or high amplitude slow wave that was positive over the vertex and central regions, and often accompanied by very low amplitude fast activity; (2) a spindle-like activity of medium amplitude at 14–16 Hz; and (3) a pattern of diffuse flattening, which is commonly called an *electrodecremental pattern*.

1.7 Epidemiology of infantile spasms

The epidemiology of infantile spasms has been reviewed by Cowan and Hudson, and by Hurst [69, 70].

1.7.1 Incidence and prevalence of infantile spasms

The main measure of disease frequency for infantile spasms is the number of cases occurring per number of live births. This is an incidence proportion, or incidence rate. Some studies have looked at cumulative incidence or period prevalence by following children through the first two years of life, or longer. These estimates are affected by deaths occurring during the period of study. All such studies of infantile spasms are rendered difficult to interpret by variations in case definition [70].

Melchior reported 113 cases identified in a Danish survey between 1970 and 1975. In order to study any effect of pertussis immunisation, they compared the distribution of age at onset with cases reported in the period 1957–67 [71]. Melchior did not state the population denominator, but it was later estimated to be between 0.25 and 0.35 per 1000 live births [72]. Riikonen and Donner studied 107 children born in the county of Uusimaa, Finland and from these estimate the incidence in the three periods 1960–66, 1967–71, and 1972–76 to be 0.42, 0.38, and 0.42 per 1000 live births respectively [72]. There was temporal variation in underlying aetiology, suggesting that the small variation in the three estimates is partly due to chance. Eeg-Olofsson and Sidenvall studied incidence in the Uppsala region of Sweden and found an incidence of 1.4 per 1000 live births in one county in the north-east of this region [73] and suggested that this cluster of very high incidence was related to the release of material from the nuclear power generator at Chernobyl. However, a later report stated an incidence range in these counties of 0.17 to 0.76 per 1000 live births [74].

A large study of the incidence of seizures in the United States by Ellenberg *et al* failed to distinguish infantile spasms from other "minor motor seizures," including tonic, myoclonic, akinetic and asymmetrical seizures [75]. Trevathan *et al* performed a population-based study in Atlanta, Georgia between 1975 and 1977, ascertaining cases from reports provided by 21 EEG laboratories and by history from children involved in a cross-sectional survey [76]. They estimated cumulative incidence at 2 years of age to be 0.29 per 1000 live births, and age-specific prevalence at 10 years of age to be 0.20 per 1000. Since not all cases of infantile spasms will have hypsarrhythmia, this is likely to be an underestimate of true incidence. With some standardisation of population denominators and exclusion of 10/269 children with onset of spasms after 1 year, Hurst estimated a prevalence for infantile spasms from the United Kingdom National Childhood Encephalopathy Study (NCES) to be 0.13 per 1000 chil-

dren aged between 2 months and 3 years [70, 77].

1.7.2 Sex distribution of infantile spasms

Some early studies suggested that males were more likely to be diagnosed with infantile spasms than females. One early study found a male to female ratio of approximately 2.25:1 (104 males and 46 females) [58]. However, a review of 444 cases from 8 earlier studies, showed an appreciably lower male:female ratio of 1.35:1 (255 males and 189 females) [18] and one recent series of infants with infantile spasms had 60 males and 56 females, a ratio of approximately 1:1 [78]. It appears that males are more likely to develop infantile spasms, but the size of this increased risk may be small.

1.7.3 Family history of epilepsy

It has been suggested that the incidence of epilepsy is lower in relatives of persons who have had infantile spasms than in relatives of persons with other forms of epilepsy [18]. Some underlying causes, such as tuberous sclerosis, are inherited and associated with other seizure types. In such cases, a family history of infantile spasms might be expected, but would depend upon the probability of an affected person having children, and people with learning difficulties tend to have lower fertility rates. There have been reports of infantile spasms occurring in twins, and in siblings in a family with X-linked mental retardation (section 1.7.6) [79, 80, 81].

1.7.4 Age at onset of infantile spasms

There is often a significant period between onset of spasms and diagnosis, and it may be difficult to distinguish antecedent developmental delay or regression from apparently antecedent developmental problems that are actually due to

this period during which clinical spasms are not recognised. In addition, it is likely that many cases have electroencephalographic abnormalities earlier still. In this thesis, I use the term *apparent lead-time to diagnosis* to indicate an elapsed period between onset of observed spasms and diagnosis. The term *lead-time to diagnosis* without further qualification indicates an elapsed period between actual biological onset of spasms or the electrographic equivalent, whether observed or unobserved.

The distribution of ages at onset of spasms is difficult to determine for several reasons. First, there is often substantial uncertainty about the apparent lead-time to diagnosis. Second, some investigators and ILAE commissions have defined upper age limits for onset of infantile spasms so that are differences due to case definition between different periods of study. Typical upper age limits are 1 year and 2 years, despite the fact that early reports included children with onset at older ages [17, 18, 34, 35, 82]. Melchior used cumulative distributions of age at onset in two time periods to investigate the potential effect of pertussis immunisation and found 6% to have onset before 2 months and 3% to have onset between 12 and 17 months [71].

Differences in case definition result in some studies having right-censored ages of onset. A recent series of 116 cases reported by Fejerman *et al*, for example, reported a median age for onset of spasms of 5.6 months and a range of 2 to 10 months. However, despite these variations in classification and eligibility for study, it seems that the median and mode months of onset of infantile spasms are in the middle of the first year of life. Few cases occur in the first two months of life, and even though reporting practices may cause bias, it seems that few cases occur after 12 months of age [78].

1.7.5 Natural history of infantile spasms

It is necessary to refer to earlier studies to make inferences about the natural history of duration and age at cessation of spasms. Without specific treatment interventions, infantile spasms may cease several weeks after onset, or may continue for several years. Jeavons and colleagues reported on 116 children, having excluded 34 children who had died while still suffering from infantile spasms or for whom there was incomplete follow-up data [58]. All of these children were followed beyond 3 years old, and some had been treated with ACTH or steroids. Spasms ceased before one year of age in 32 (28%); before 2 years of age in 57 (49%); before 3 years of age in 75 (65%); in 86 (74%) by 4 years of age; and in 98 (85%) before 5 years of age. The proportions with continued spasms would be smaller today, since there are more effective first-line and second-line treatments. Prognosis is discussed more fully in Section 1.7.7.

1.7.6 Underlying disorders and aetiology

Issues relating to the classification of cases of infantile spasms into aetiological subgroups are discussed in section 1.4.2. Since there has been variable usage of the terms *cryptogenic* and *idiopathic*, in this section I will refer to the terms collectively as *non-symptomatic* unless a more specific usage is appropriate.

In case series described before cryptogenic and idiopathic forms of infantile spasms were distinguished, the reported proportions with non-symptomatic infantile spasms ranged from 15% to 56% [40, 41]. Lacy and Penry reviewed ten large studies performed before 1973, and found that the mean proportion with non-symptomatic spasms was 40% [18]. A review of studies reported between 1973 and 1982 reported the proportion of cases with non-symptomatic infantile spasms to range between 15% and 53%. The population-based study by Trevathan *et al* reported infants notified by EEG departments in the Atlanta

area. It found that half of identified cases were classified as non-symptomatic. Variably defined favourable outcomes in children classified as having non-symptomatic infantile spasms have been reported in proportions ranging from approximately one-fifth (21%) to more than half of cases (58%) [36].

It is almost certain that, as neuroimaging and genetic diagnostic techniques become more sensitive, a higher proportion of cases will be classified as symptomatic at the time of diagnosis of infantile spasms. The development of magnetic resonance imaging, for example, has led to the recognition of previously undetectable cerebral cortical dysplasias, and the development of more sensitive imaging protocols performed by machines with higher magnetic field strength further increases the detection of even more subtle lesions.

Proportions of cases with specific underlying causes

Cases with specific underlying aetiologies are reviewed by Dalla Bernardina and Dulac [38], with further categorisation of symptomatic cases into groups relating to timing of the aetiological agent's action: prenatal, perinatal, or postnatal causes; and, independently, into groups described as clastic, degenerative (or metabolic), malformative, and cryptogenic. They discuss the issue of competing potential underlying causes, and also a specific problem relating misclassification of cases considered to have a postnatal cause due to immunisation. Since the report of findings from the National Childhood Encephalopathy Study performed in the United Kingdom between 1976 and 1979, the causal link between immunisation and infantile spasms is considered to be weak and the apparent association to be confounded by the often coincident timing of immunisation schedules and the age-dependent propensity to develop infantile spasms [77, 39].

A neuropathological review of 50 cases from Vienna, Austria combined with 214 other reported cases suggested that one-third (30–34%) of cases of

infantile spasms with early fatal outcomes were due to cerebral malformations but, like other studies to date looking at underlying conditions, this was not a population-based study [83]. Also, there is an obvious selection bias associated with including only cases subject to postmortem examinations. This same study reported that 36 to 40% of cases were associated with perinatal brain damage, and that 17% were associated with underlying metabolic disorders.

Tuberous sclerosis is known to be a common underlying cause of infantile spasms, but estimates of its relative frequency also vary greatly. A review by Curatolo reported that tuberous sclerosis was identified as being the underlying cause in between 7% and 25% of symptomatic cases, and a study he performed with colleagues reported a prevalence of 11% in a series of 164 infants undergoing CT scanning [84, 85].

Specific underlying causes

There are many disorders that are found to coexist with infantile spasms and that might be considered to cause the spasms and the associated developmental delay. The combination of the epileptiform EEG with delayed or regressing development is often described as a *epileptic encephalopathy*. Thus, a number of putative causal mechanisms are invoked to describe events surrounding infantile spasms. Underlying conditions, genetic predisposition, or acquired diseases cause an epilepsy condition, and those underlying or acquired factors might cause developmental delay or regression, but so might the epilepsy itself. This thesis often uses the term *underlying condition* to describe the underlying disorder, genetic predisposition, or acquired disease, rather than any term that has causal connotations, such as *aetiology* or *underlying cause*.

Some of these conditions may coexist with infantile spasms by chance. Histidinemia, for example, is a relatively common metabolic disorder, and has only once been described in association with infantile spasms [86, 87]. The

following underlying conditions have been described in association with infantile spasms and may have a causal role. A broad outline of these conditions and citations are given by Aicardi, and by Dalla Bernardina and Dulac [26, 38]. The list below is not exhaustive, but gives an idea of the range of conditions with which infantile spasms have been described. References are given for underlying conditions that are not described in the above reviews.

Brain neoplasms: benign and malignant tumours; hypothalamic hamartoma.

Endocrine, metabolic, and toxic: histidinemia [86]; histidinuria; hyperornithinemia, hyperammonemia and homocitrullinemia (HHH syndrome); lead toxicity; Leigh disease; lithium toxicity; neonatal adrenoleukodystrophy; nonketotic hyperglycinemia; progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO syndrome); phenylketonuria; pyridoxine dependency; pyruvate carboxylase deficiency; sudanophilic leukodystrophy.

Nervous system infections: bacterial meningitis (meningococcus, pneumococcus); pertussis [88]; prenatal infections (cytomegalovirus, rubella, syphilis; toxoplasmosis) viral encephalitis (adenovirus, enterovirus, herpesvirus) [88].

Cerebrovascular: acute dehydration; cardiac arrest; cardiac surgery; cerebrovascular infarction; intraventricular haemorrhage; subarachnoid haemorrhage.

Perinatal: abruptio placentae; brainstem gliosis; hydranencephaly; hypoxic-ischemic encephalopathy; intrauterine growth retardation; leukomalacia; maternal diabetes mellitus; maternal pre-eclamptic toxemia; multicystic encephalomalacia; porencephaly; ulegyria.

Congenital: agenesis of corpus callosum; Aicardi syndrome; cortical dysplasia, megalencephaly; cortical sublaminar heterotopia; costo-oculo-facial syn-

drome (COFS); Down syndrome [37]; hemimegalencephaly; holoprosencephaly; incontinentia pigmenti; linear nevus syndrome; lissencephaly (Miller-Dieker syndrome, isolated lissencephaly sequence, and X-linked lissencephaly); neurofibromatosis type 1 (NF1); Rett syndrome; schizencephaly; tuberous sclerosis (TS); Sturge-Weber syndrome; and X-linked disruption of the serine/threonine kinase 9 gene [89]; X-linked mutation of the Aristaless-related homeobox gene (ARX) [90].

External injury: accidental injury; drowning injury [91]; non-accidental injury; subdural haemorrhage.

Reiter *et al* have reported infantile spasms occurring in siblings in 2 families. In one family the infantile spasms occurred in monozygotic twins. [80] One of the four cases had later delayed development. A contentious issue has been whether pertussis immunisation causes infantile spasms and other forms of encephalopathy in infancy [71, 92]. Hrachovy *et al* reported HLA types in 29 children with infantile spasms with those of 218 healthy controls and found a higher prevalence of the Class II antigen, HLA-DRw52, though the statistical analysis did not involve any adjustment for multiple testing. An earlier study on 21 children with infantile spasms by Howitz and Platz showed no association of infantile spasms with Class I HLA antigens.

1.7.7 Prognosis in infantile spasms

There can be little doubt that outcomes in infantile spasms are strongly related to underlying conditions. In general, it is suggested that cases classified as symptomatic have poorer outcomes, but there is variation in this classification used between studies, and any symptomatic group will consist of a variety of conditions with potentially different prognoses. Convulsive seizures pre-

ceding the onset of spasms, or other convulsive seizures occurring during the same period as the spasms, are thought to be associated with a higher chance of seizures in later life. Similarly, preceding developmental delay is thought to be associated with poorer later development.

Matsumoto *et al* sought follow-up information about development at the age of 6 years on 262 children treated between 1963 and 1972 in Nagoya, Japan [40]. Information was available for 162 (62%) cases. Forty-eight (18%) had died, 32 (12%) before the age of 6 years. They received replies from 60/116 (52%) families whose children had been lost to follow-up. Of the 162 cases successfully followed-up, they classified 18 (11%) as *cryptogenic* by criteria that many would be more appropriate for classification as *idiopathic*. Ninety-eight (60%) were classified as symptomatic and 46 (28%) as *doubtful*. They suggested that later development was poorer if there was a prenatal or perinatal aetiology, or structural damage evident on pneumoencephalography. The magnitude of these effects are difficult to quantify.

Matsumoto *et al* also suggested that a longer lead-time to treatment was associated with poorer prognosis for development in cases they had classified as *cryptogenic*, though this may be affected by biases related to incomplete information and misclassification. The argument that longer lead-time to diagnosis modifies prognosis is not proven, and some authors have cited the absence of evidence in defence of study designs that involve delays in treatment [93, 94, 95].

Dalla Bernardina and Dulac have proposed four broad categories of aetiology – *clastic*, *degenerative*, *malformation*, and *cryptogenic idiopathic* – and that, by classifying cases into one of these four groups or as *idiopathic*, it is possible to identify five patterns of prognosis [38]. First, extensive malformation or destruction of the brain are likely to produce protracted infantile spasms. Second, cortical lesions, such as those found in tuberous sclerosis or hypoxic-

ischaemic encephalopathy, are associated with multifocal epilepsy. Third, a single focus, such as might be found with porencephaly, cortical dysplasia, or some cases of tuberous sclerosis, will cause focal epilepsy. Fourth, they suggest that Lennox-Gastaut is a likely outcome in cases with cryptogenic forms of infantile spasms. And fifth, they suggest that cessation of seizures and normal subsequent development occurs with idiopathic infantile spasms.

Survival and mortality

As with prognosis for development and convulsive seizures, death rates are strongly related to underlying disorders. One early study of 7 children reported reported that all seven children had died by 3 years of age [96]. One cohort of 150 children was followed by Jeavons *et al* to the age of 12 years, by which time 33 (22%) had died [58]. And an early study by Gibbs *et al* reported death in 11 of 103 children [41]. The commonest stated cause of death was aspiration pneumonia, though this is likely to be causally related more to underlying neurodevelopmental problems than to the spasms themselves. It is possible that the risk of death due to infective causes was modified by treatment with ACTH.

Neurodevelopmental outcomes

The neurodevelopmental outcomes of 64 infants treated with ACTH or prednisone were reported Glaze et al [97]. The average age at follow-up was 50 months. Three (5%) had died, and 41 (64%) had significant neurodevelopmental problems, with an IQ of less than 50. Of 8 children with no identified underlying cause, 3 had normal development or minimal neurodevelopmental problems at follow-up. Other seizures occurred in 34 (53%).

1.8 Treatment of Infantile Spasms

There is scepticism about the quality of evidence informing the choice of first-line treatment for infantile spasms. This scepticism was expressed amusingly in 1995 by the Archivist of *Archives of Disease in Childhood*, who ironically implies that inappropriate subgroup analyses, combination treatments, and anecdotal opinion are all too common [98].

> Infantile spasms should be treated with nitrazepam and a month of corticotrophin followed by two months of prednisolone unless the year ends with an odd number and your grandmother was born on a Wednesday, when sodium valproate and prednisolone for six weeks are de rigeur, although you could make do with vigabatrine [sic] and three weeks of hydrocortisone if your favourite colour is blue and Jupiter is about to collide with Mars.

In the United Kingdom in the latter half of the 1990s, the most common first choice treatments for infantile spasms were hormonal treatments, such as oral prednisolone or ACTH, and vigabatrin. Sodium valproate or valproic acid are still occasionally used as a first-line treatment. Pyridoxal phosphate (or pyridoxine; vitamin B6) has been used in several studies, and is popular in Japan, where it is often combined with sodium valproate or low-dose ACTH. Surgical procedures are considered if medical treatments are ineffective and there is a focal lesion that is thought to trigger the seizures. Newer drugs, such as topiramate and zonisamide, have been investigated as add-on treatments, but reports have not suggested them to be superior to hormonal treatments or vigabatrin. These treatments are discussed in more detail in section 1.8.1.

Efficacy criteria between studies of infantile spasms may vary markedly, and some studies do not state explicit definitions for even the main outcome measure. For example, the measurement may be made after several weeks or

several months, or no time limit at all may be stated. Also, some definitions of outcome measure include other requirements, such as resolution of hypsarrhythmia. Outcomes such as mean reduction in number of spasms are likely to be less valuable than cessation of spasms, since any continual spasms indicate continuation of an underlying disease process that is likely to interfere with development.

The collective term generally used for hormonal treatments is *steroids*. However, ACTH and its synthetic derivatives do not have a steroid structure and, although the scientific principal of parsimony would support the idea that ACTH acts primarily via an effect upon increased adrenal production of endogenous corticosteroids, this is not certain and this assumption has been challenged [99]. For these reasons, in this thesis the term *hormonal treatment* is used as a collective term for treatment with ACTH, derivatives of ACTH, or corticosteroids. Although thyrotrophin-releasing hormone (TRH; thyrotropin (US)) has been used to treat infantile spasms, no reference to this is intended when referring to *hormonal treatment* [100].

1.8.1 Brief review of treatments for infantile spasms

ACTH moieties: Pentella *et al* treated 5 cases of infantile spasms with an $ACTH_{4-9}$ analogue and found no evidence of any treatment effect. [101] Willig and Lagenstein treated 7 cases with $ACTH_{4-10}$, again without any evident treatment effect [102]. The $ACTH_{1-24}$ analogue tetractosactide (cosyntropin) is one of the drugs studied in UKISS and is discussed in section 1.9 [103].

Barbiturates: Riikonen *et al* reported use of brief thiopentone anaesthesia, using an intravenous dose of 30 mg/kg, in five cases of infantile spasms. Three patients had EEG changes of burst-suppression, but spasms relapsed and the treatment was not considered to be very effective [104].

Benzodiazepines: These were a popular treatment in the 1960s, with nitrazepam finding particular popularity. The series of Völzke *et al* reported cessation of spasms after treatment for one week in 11/24 (46%) of cases [105]. De Negri *et al* found a poor response to high-dose rectal diazepam in 10 children with hypsarrhythmia, in contrast to good EEG responses in children with electrical status epilepticus in sleep (ESES) [106].

Corticotrophin-releasing factor antagonists: This has been studied in a phase II trial by Baram, but its effect was not convincing [107]. This lack of effect is possibly due to failure of the drug to cross the blood-brain barrier.

Dexamethasone: Treatment with depot dexamethasone is discussed in section 1.8.3 [108].

Felbamate: This is recognised as a treatment of a range of generalised and focal onset seizures, though its use is limited because of risks of aplastic anaemia and hepatotoxicity. A study by Hosain *et al* suggested that felbamate as add-on therapy might reduce frequency of spasms, but the study did not include any controls or report a reliable outcome related to cessation of spasms [109].

Ganaxolone: There has been one phase II trial of the neuroactive steroid, ganaxolone, which included children with infantile spasms [110]. Ganaxolone binds to the GABA receptor complex but has no steroid hormonal activity. It had some effect on the frequency of spasms in children who had not responded to other treatments, but had no significant effect on cessation of spasms.

Immunoglobulins: One study looked at 7 patients with Lennox-Gastaut syndrome, some of whom had had infantile spasms [111]. Another study reported 11 children with infantile spasms, 6 of which were classified as cryptogenic

[112], and one study reported findings in 15 children, 3 of whom had infantile spasms [113].

Lamotrigine: A study reported by Veggiotti *et al* showed little effect of lamotrigine upon infantile spasms in 30 patients, all of whom had already received combinations of steroids ($n = 21$), vigabatrin ($n = 23$), sodium valproate ($n = 29$), and benzodiazepines ($n = 26$) [114]. After 3 months of lamotrigine treatment, spasms were reported to have stopped in 5/30 (17%), and to have continued with no substantial change in frequency in 19/30 (63%).

Methysergide and α-methylparatyrosine: Methysergide is a serotonin (5HT) receptor blocker, and α-methylparatyrosine is a competitive blocker of tyrosine hydroxylase and hence of catecholamine synthesis. Methysergide has been used to treat myoclonic conditions such as dyssynergia cerebellaris myoclonica (Ramsey Hunt syndrome), paramyoclonus multiplex, and L-dopa induced myoclonus [115]. Hrachovy *et al* believed infantile spasms to be due in part to increased brainstem adrenergic or serotonergic activity [94]. They studied 24 children, 23 of whom were classified as symptomatic, and defined their primary outcome as cessation of spasms and resolution of hypsarrhythmia after three weeks of treatment. As first-line treatment, 12 were given methysergide and 12 were given α-methylparatyrosine. Only 3/24 had a primary response, 2 of whom had received α-methylparatyrosine, and one had an early relapse of spasms. They considered this to be an ineffective treatment.

Naloxone: Nalin *et al* found no substantial effect of naloxone on infantile spasms in 5 chidren [116].

Nitrazepam: There has been one study of nitrazepam versus ACTH, though the results are difficult to interpret because of co-administration of other anti-

epileptic drugs, including valproic acid [117]. Response was defined as a 75–100% reduction in spasms.

Pyridoxine (vitamin B_6): The term *vitamin* B_6 is used to describe pyridoxine, pyridoxal, and pyridoxamine, but the Council on Pharmacy and Chemistry has assigned the name pyridoxine to the vitamin [118]. Pyridoxine is the primary alcohol, with pyridoxal having an aldehyde group at the 4-position of the pyridine nucleus, and pyridoxamine having an aminoethyl group at this position. Studies by Ohtsuka *et al* have suggested that infantile spasms might respond to treatment with pyridoxine. In their initial study, they found that 15/118 (13%) of cases responded to treatment with cessation of spasms, though they did not state how soon after administration of pyridoxal phosphate the cessation occurred [119]. They used a tryptophan load test to identify whether any of the children had a deficiency of vitamin B_6, and found that there was a slightly increased excretion of xanthurenic acid in only one case. Cumulatively, they treated 216 infants with pyridoxine between 1969 and 1998, and found that 30 (14%) responded with cessation of spasms for a period of 1 month or longer [120]. In some cases, the pyridoxine was added to treatments that had been ineffective. With such a low response rate and ill-defined time-to-response, it is difficult to determine what proportion of these responses might be spontaneous improvement. As well as a potential treatment effect in any case of infantile spasms, pyridoxine has a specific effect in children with pyridoxine-dependent seizures [121, 122].

Sulthiame: This is a sulphonamide derivative and an inhibitor of carbonic anhydrase. A non-randomised add-on study of pyridoxine and sulthiame reported cessation of spasms within 7 days in 7/12 males with newly diagnosed infantile spasms [123].

Tetrabenazine: This inhibits the reuptake and storage of monoamines, and is sometimes used to treat severe tardive dyskinesia [124]. Hrachovy *et al* investigated its effects in infantile spasms, again exploring the hypothesis that an important factor is an imbalance of brainstem neurotransmitters [125]. They studied 12 children, 5 of whom had previously received ACTH and prednisone, but none showed any benefit.

Thyrotrophin-releasing hormone (TRH): A study by Matsumoto *et al* used a non-randomised design and compared cessation of spasms after 16 days of treatment with TRH and ACTH. The TRH group had 7/13 (54%) responses compared with 15/20 (75%) in the ACTH group [100]. These were not contemporaneous groups: the TRH-treated group was studied during a later period than the ACTH-treated group. Four children in the TRH had recurrence of spasms within 3 months.

Tiagabine: A small study has reported the use of tiagabine in infantile spasms but it has shown little treatment effect [126].

Topiramate: Glauser *et al* studied the effects of topiramate as treatment in 11 children who had not responded to treatment with two established drugs, though the established drugs did not include vigabatrin [127]. The initial treatment was tapered and stopped over one week unless it was a benzodiazepine or phenobarbital, in which case it was continued. Five children met the primary response criteria of cessation of spasms and absence of hypsarrhythmia on 24-hour video EEG. Two of these responded within 14 days after starting treatment with topiramate, but the other 3 responded between 1 and 3 months.

Typhoid vaccine: Garcia de Alba *et al* studied the effects of fever after giving a vaccine to typhoid and paratyphoid (TBA) on 4 children with infantile

spasms that had not responded to treatment with ACTH, prednisolone, nitrazepam and other treatments. They reported improvement and resolution of hypsarrhythmia [128].

Valproic acid and sodium valproate: This is available as a sodium salt or acid (sodium valproate (sodium dipropylacetic acid) or valproic acid (*n*-dipropylacetic acid)). It was a popular choice in the late 1980s and early 1990s, and remains a common choice as second- or third-line treatment today. Pavone *et al* reported cessation of spasms at 20 days in 4/18 infants treated with valproate 20 mg/kg/day [129]. There is an association with idiosyncratic liver dysfunction that can be fatal, and this has reduced enthusiasm for using it. One non-randomised study of 42 children treated with doses of valproate around 10 times that conventionally used for the treatment of epilepsy, with a range of 100 to 300 mg/kg/day, reported that 33 (79%) had resolution of hypsarrhythmia by 21 days, with 8 (19%) later relapsing [130]. One group reported good responses to a combination of sodium valproate and oral hydrocortisone [131].

Zonisamide: Suzuki *et al* used zonisamide as add-on therapy for 11 cases of infantile spasms that had not responded to treatment with pyridoxine. By 5 days of treatment, 4/11 had cessation of spasms and resolution of hypsarrhythmia, but 2/4 relapsed within 6 weeks [132]. Yanai *et al* studied the effects of zonisamide add-on or monotherapy in 27 children, with cessation of spasms in 9/27 (33%) [133]. Mean time to cessation of spasms was 5 days, and relapse occurred in 4/9 cases.

Ketogenic Diet: The ketogenic diet has been used with some success in infants, including some with infantile spasms [134].

Surgical treatment: Surgical treatment has become popular for older infants and children who have focal lesions and who have not responded to treatment with more conventional drugs. The results of studies vary widely, probably because of differences in selection criteria and the age at which surgery was performed. Since surgical treatment is only considered when several medical treatments have failed, this area is not explored in this thesis.

1.8.2 An overview of hormonal treatments

The term *steroid* refers to chemicals that have a particular four-ring structure that includes 21 carbon atoms. The term *corticosteroid* refers to chemicals with steroid structures that are produced by the adrenal cortex, and to analogues of these chemicals. There are two subgroups of corticosteroids: mineralocorticoids, which have relatively more potent effects upon electrolyte balance within the body; and glucocorticoids, which have structural characteristics that seem to confer greater anti-inflammatory effects. Glucocorticoids generally have a Δ-4,3-keto-11β,17α,21-trihydroxysteroid structure. Subtle modifications of this structure affect anti-inflammatory and other activity.

Cortisol, which is produced in the adrenal cortex, has a single bonded hydroxyl group at the 11th carbon. Cortisone is identical to cortisol but has a double bonded oxygen molecule in place of the hydroxyl group on the 11th carbon. Hydrocortisone is structurally identical to cortisol, but is a term reserved for the synthetic preparation that may be administered as a drug. Prednisolone is identical to cortisol apart from the presence of an extra double bond. This minor structural difference makes prednisolone more active than cortisol. Prednisone is, similarly, a structural analogue of cortisone. Other glucocorticoids include dexamethasone, which has an alpha-methyl group on carbon 16, and betamethasone, which has a beta-methyl group on carbon 16.

Glucocorticoids are commonly used to suppress inflammatory reactions.

They work in part by an effect upon white blood cells, generally causing a fall in the peripheral lymphocyte count and a rise in the neutrophil count [103]. However, the exact mechanisms of their effects are not fully known. Potential mechanisms of effect include: impairing opsonisation of antigens; inhibiting superoxide production by neutrophils; impairing the production of leukotrienes and prostaglandins; interrupting cell-to-cell communication by altering the release of cytokines; and altering inflammatory cell adhesion to and migration through the vascular endothelium.

The hypothalamo-pituitary-cortical axis is the system of hormones and hormonal transport mechanisms that regulate the levels of steroids in the body. The hypothalamus produces corticotrophin-releasing hormone (CRH). CRH travels to the anterior pituitary gland and stimulates production of adrenocorticotrophin (ACTH). Corticotrophin is the synthetic analogue of ACTH that may be given as a drug, but this is often referred to without confusion as ACTH. ACTH regulates the production of glucocorticoids by the adrenal cortex. Both CRH and ACTH are polypeptides [103].

1.8.3 Steroid treatments other than prednisolone

Prednisolone and prednisone are the most commonly used steroid treatments of infantile spasms, but dexamethasone and hydrocortisone have also been used.

Dexamethasone

Yamamoto *et al* treated 5 cases of infantile spasms with dexamethasone palmitate (liposteroid) depot preparation using a regimen of 7 injections over a period of 3 months [108]. They compared this treatment with 5 children treated with ACTH 25 micrograms per kilogram per day given for 6 weeks. In all

cases, spasms stopped and hypsarrhythmia resolved within 6 to 8 weeks, though relapses or partial seizures were later noted in 3 patients in each group.

Hydrocortisone

Hydrocortisone is structurally equivalent to endogenously produced corticosterone, but the term *hydrocortisone* is reserved for the administered drug. It has been used in studies in France. For example, it was used in the trial of Chiron *et al* that compared the effects of hydrocortisone and vigabatrin in children with infantile spasms and tuberous sclerosis [16]. Since hydrocortisone is identical to endogenously produced corticosterone, it might be argued that any ACTH-induced effect mediated via adrenal steroid production is most closely mimicked by administration of hydrocortisone. However, it has generally not been used to treat infantile spasms in the UK or the US.

1.8.4 Rationale for hormonal treatments in infantile spasms

The use of hormonal treatments is largely empirical, though was in part suggested by early observations that they are effective in some forms of epilepsy [135]. Robinson suggested in 1985 that this empiricism was likely to persist for a long time [115]. He also suggested that early treatment of cryptogenic cases of infantile spasms resulted in improved developmental outcome.

1.9 ACTH and tetracosactide

Adrenocorticotrophic hormone (ACTH), which is also known as corticotrophin and corticotropin, is a polypeptide chain of 39 amino acids produced by the basophilic cells of the anterior pituitary in response to stimulation by corticotrophin-releasing hormone (CRH), which is also known as corticotropin-releasing factor (CRF). The biological activity of ACTH resides in the 24 amino

acids at the N-terminal end of the polypeptide chain, and these 24 amino acids are the same in humans, sheep, cows and horses.

ACTH stimulates production of steroids in the adrenal glands by a mechanism that involves 3,5-adenosine monophosphate (cyclic AMP; cAMP) and which regulates the rate-limiting step of steroid production from cholesterol. The main products of this stimulation are cortisol, which when administered as a drug is called hydrocortisone, and corticosterone. In addition, ACTH stimulates the production of small amounts of several androgenic steroids and aldosterone.

The potency of ACTH and its synthetic analogues have traditionally been determined by an assay of adrenal ascorbic acid depletion in rats whose pituitary glands have been removed. However, the validity of such assays has been questioned and there are few comparisons of ACTH analogue potency [136].

Tetracosactide is the polypeptide chain containing the 24 biologically active N-terminal amino acids of corticotrophin. The former British Approved Name (BAN) was tetracosactrin. The new BAN is now the same as the Recommended International Non-proprietary Name (rINN): tetracosactide. Two other generic names, cosyntropin and tetracosapeptide, appear in North American texts [137, 138]. The actions of tetracosactide are similar to that of endogenous or administered ACTH, but it is thought to have less potential for causing immunological reactions and greater potential antigenic action residing in the C-terminal amino acids, 22–39.

The potency of tetracosactide is said to be such that 0.25 mg is equivalent to 25 IU of corticotrophin. In its standard formulation, it is rapidly absorbed after being given intramuscularly, and larger doses are associated with longer duration of stimulated steroid levels. Thus, alternate day dose frequency seems to be effective. It is rapidly removed from the plasma by several tissues, but

little is known about its distribution and metabolism. A depot formulation is also available. One regimen for depot tetracosactide was suggested by Lerman and Kivity: 1 mg IM alternate days for 2 weeks; then 1 mg twice a week for 2 weeks; then 1 mg weekly for 4 to 6 weeks; then 0.5 mg weekly for 2 weeks [139]. With this regimen, the total duration of tetracosactide treatment is 10 to 12 weeks. However, this was only Stage I of their suggested regimen for the treatment of infantile spasms. Stage II required "prednisone by mouth for at least six months," 10 mg/day for the first month and then tapering.

1.9.1 Effectiveness of ACTH and tetracosactide

Reports in the 1940s and 1950s about the use of oral corticosteroids and ACTH in seizure conditions disagreed about whether the seizures improved or worsened. In 1950, Klein and Livingston reported that seizures improved in 4 of 6 children who had not responded to any of the standard treatments available at that time [135]. At the end of that decade, several reports appeared of successful treatment with ACTH [10–15] and with oral corticosteroids [13, 14]. These studies were case series rather than controlled trials with well-specified outcomes. The mechanism of this therapeutic effect of ACTH has not been determined.

There are no large studies of treatment of infantile spasms that have aimed specifically to assess the efficacy of tetracosactide, although studies of cases that have been treated with animal-derived and synthetic forms of ACTH have looked at aspects of safety of synthetic preparations that have included tetracosactide.

1.9.2 Safety of ACTH and tetracosactide

There are many potential adverse effects associated with treatment with ACTH [140, 141]. Suppression of the immune system predisposes to infection, and clinical signs may be masked because of suppressed inflammatory responses, a combination that may be rapidly fatal [142]. Reported infections include pneumonia and subcutaneous abscess [100]. Adrenal suppression may occur during treatment of children with infantile spasms, [143, 144, 145] and there are risks of hypertension and glucose intolerance, though these might not be associated with any long-term morbidity. Other problems reported during treatment of infantile spasms with corticotrophin or synthetic ACTH include cardiac hypertrophy and enlargement of a cardiac rhabdomyoma [146, 147, 148]. Investigators have also reported metabolic disturbances such as hypokalaemia, hypocalcaemia, hypophosphataemia and hypomagnesaemia [149, 150, 151]. Zeharia *et al* reported hyperkalaemia in two children after stopping treatment with depot tetracosactide [152]. Their treatment regimen was a modified form of that described by Lerman and Kivity, the planned duration of depot tetracosactide treatment being 8 weeks [139]. In one case, treatment had stopped after 2 weeks because of gastroenteritis. Another recognised complication is cataract [100]. Glaze *et al* reported evidence of brain shrinkage after two weeks of treatment with ACTH or prednisone in two-thirds of children, though this is not known to be associated with any long-term adverse effect [153].

Early reports suggested high incidences of adverse effects in children treated for infantile spasms with corticotrophin and, though numbers were too small for firm inferences to be made, these tended to be higher with synthetic ACTH preparations such as zinc tetracosactrin (Synacthen® Depot and S-Cortrophin® Depot) [140, 154, 155]. The duration of ACTH treatment at that time was often

several months, and the risks associated with synthetic ACTH preparations are likely to be smaller now that shorter duration and alternate day regimens are preferred.

Bovine-derived ACTH was withdrawn from the UK market in 1998 and the ACTH preparation now commonly used to treat infantile spasms is a depot tetracosactide. No formal statement was made of reasons for its withdrawal, but this may have been because of its higher antigenicity or because of potential risks of transmission of new variant Creutzfeld-Jakob disease (nv-CJD).

Riikonen and Donner reviewed 162 children who had been treated for infantile spasms treated with ACTH preparations between 1960 and 1972 [140]. The Helsinki hospitals participating in this study used long-acting ACTH preparations and two synthetic forms of zinc tetracosactide (Synacthen® Depot and S-Cortrophin® Depot). Until 1969, the treatment regimens used 40 units for 3 weeks, 20 units for 2 weeks, and then a one-week taper. After 1969, most children received higher doses: initially 120 to 160 units for 3 weeks, then 60 to 80 units for 2 weeks, and then a one-week taper.

The study reported adverse effects in 60 (37%) of children; and serious adverse effects in 24 (15%), of which 8 (5%) were fatal. Six of the eight fatal deaths occurred approximately 6 weeks after treatment started. Six of the children died of pneumonia, four of whom had identified causes: *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli,* and *Pneumocystis carinii.* There were also reported non-fatal cases of pneumonia due to *Staphylococcus aureus* and *Pneumocystis carinii.* The presence of these organisms strongly suggests immunosuppression, the most likely cause of which was hormonal treatment.

Plasma cortisol levels were measured in only 4 children, and the reasons for selecting these 4 children for this investigation are not stated. The measurements were timed to occur 2 days before the hormonal treatment was due to stop, and 3 of the 4 children had low or unrecordable levels of cortisol.

Infections occurred in 35/139 (25%) of children treated with ACTH preparations, and in 10/23 (45%) of children treated with synthetic ACTH. These differences are not statistically significant ($\chi^2_{(1)} = 3.29$; $P = 0.08$), but the number of children treated with synthetic forms of ACTH was small. Infections occurred in 22/97 (23%) of children treated with lower doses, and in 21/54 (39%) of children treated with higher doses. These proportions are significantly different ($\chi^2_{(1)} = 4.47$; $P = 0.034$). Unfortunately, the data presented in table 2 of that paper do not indicate whether the 11 children who were given a combination of ACTH and dexamethasone received higher or lower doses of ACTH, so this re-analysis is incomplete. Also, the data do not allow an analysis of possible effect-modification of any effect of higher dose by the type of ACTH used.

Adverse effects associated with treatment with tetracosactide are similar to those associated with treatment with animal-derived ACTH [140, 149]. An apparently worse safety profile may be due to using relatively high doses [154, 155]. One study specifically reported impairment of polymorphonuclear neutrophil function in children with infantile spasms treated with synthetic ACTH [156]. Brombacher *et al* reported allergic reactions to Synacthen Depot but not to the β1–24 moiety alone, suggesting that combination with the zinc complex contributes to allergenicity [157].

1.9.3 ACTH and tetracosactide regimens

Dosage regimens for corticotrophin have ranged widely in both dose and duration. Hrachovy *et al* used 20 IU/day for 2 weeks followed by a one-week tapered reduction in dose in one study [93], but had earlier used up to 40 IU/day for six weeks [158]. A more aggressive regimen, reported by Riikonen and Donner, is up to 160 IU/day for 3 weeks, then up to 80 IU/day for a further 2 weeks, and a 1-week taper [140]. Lerman and Kivity report a starting dose of

up to 100 IU/day that is reduced after spasms stopped and is continued for up to 6 months [139].

One study suggested that infections were commoner in children treated with higher compared with lower doses [140]. A retrospective study of the same children suggested that a higher dose of 120 IU/day was no more effective than a lower dose of 20 to 40 IU/day [159]. A randomised trial comparing higher dose, longer duration of treatment with lower dose, shorter duration reported no significant differences in efficacy, but a significant difference in the proportions with reported adverse effects [160]. Because of the study design, we cannot infer whether the higher proportion of adverse events are associated with the higher dose or the longer duration of treatment.

1.10 Prednisolone and prednisone

1.10.1 Effectiveness of prednisolone and prednisone

It is thought that frequent administration of oral corticosteroids is required to maintain levels similar to those that would be produced by the administration of ACTH or its derivatives [161]. One non-randomised study of treatment of infantile spasms suggested that ACTH has a better treatment effect than prednisone [141]. Studies that compare these treatments using randomly allocated treatments are discussed below.

In children, drug doses are often calculated by body weight or body surface area, the latter being calculated from information about weight and height. However, some investigators have argued that higher doses of oral steroids are relatively safer in children, and that such doses are required in the treatment of infantile spasms in order to obtain a therapeutic effect equivalent to that of ACTH preparations [162].

1.10.2 Safety of prednisolone and prednisone

The main adverse effects reported in children are related to fluid and electrolyte imbalance, and infection. Infectious and immune complications include increased susceptibility to infection, an increased risk of infection with opportunistic organisms, and a suppressed inflammatory response to infections that masks clinical signs. Fluid and electrolyte disturbances include: fluid and sodium retention; hypertension; potassium loss; and hypokalaemic alkalosis. The risks of adverse effects attributable to prednisolone are likely to be related to dose and duration of treatment. In adults, prednisolone doses of less than 40 mg/day for less than three weeks are thought not to confer an important risk of suppression of the hypothalamic-pituitary-adrenal (HPA) axis. However, suppression of adrenal responses has been shown to occur in adults after short-term, high-dose treatment with glucocorticoids [163]. HPA axis suppression can lead to acute adrenal insufficiency, hypotension, and death. Other endocrine and metabolic adverse effects include cushingoid appearance, weight gain, increased appetite, impaired carbohydrate tolerance, and a negative body balance of calcium and protein.

Anaphylactic reactions due to treatment with prednisolone have been reported, but are rare.

1.11 Vigabatrin

Vigabatrin is an irreversible inhibitor of the enzyme gamma-aminobutyric acid transaminase [164]. This enzyme degrades gamma-aminobutyric acid (GABA), which is a major inhibitory neurotransmitter within the human central nervous system. The design and development of vigabatrin was motivated by a desire to make GABA more available in the central nervous system. Since most earlier antiepileptic pharmaceutical preparations arguably owed more to

serendipity than focus on a specific mechanism and structure, vigabatrin has been described as the world's first designer antiepileptic drug [165]. The international birth date (IBD) of vigabatrin was 22 September 1989, and the first country to approve its marketing was the United Kingdom.

1.11.1 Effectiveness of vigabatrin

Several early studies of vigabatrin treatment of children with epilepsy suggested that it had best effect in partial seizures and infantile spasms [166]. Two randomised studies have compared vigabatrin with hormonal treatment of infantile spasms, and there have many series and non-randomised studies. A retrospective study of 192 children with infantile spasms treated with vigabatrin showed that over two-thirds stopped having spasms during the initial phase of treatment [167, 168]. The proportions responding were higher in the lowest age group and in infants with tuberous sclerosis. Of those who responded, approximately one-fifth had relapse of spasms and one-fifth developed other seizure types.

Chiron *et al* studied 70 children who had failed to respond to various other treatments of infantile spasms and reported the effects of treatment with vigabatrin [169]. Of these 70 children, 47 (67%) were less than a year old and 43 (61%) had previously been treated with corticosteroids. Spasms ceased in 29/68 (43%) of children, and reduction of greater than 50% in spasm frequency was reported in 46/68 (68%) of children.

1.11.2 Visual field losses associated with vigabatrin

Since it was thought to be the safer drug, there was an argument for choosing vigabatrin as first-line treatment of infantile spasms and reserving hormonal treatment for children who did not respond to vigabatrin, even if vigabatrin

was rather less effective in stopping spasms. Adverse effects reported in earlier studies were restricted to non-serious effects such as drowsiness, irritability, and hypotonia.

In 1997, investigators reported several cases of visual field loss in adults treated with vigabatrin [170] and we now know that there is a substantial risk of such visual field losses. Although there may be important sampling biases that make risk estimates high, studies of adults treated with vigabatrin suggest that visual field losses may develop in one-third to one-half of cases [171, 172, 173]. Vigabatrin seems also to affect colour vision and visual acuity [172]. Some electrophysiological measurements, such as the electro-oculographic Arden index, are abnormal during treatment, but do not predict visual field losses [173].

Visual field losses due to vigabatrin are persistent and probably irreversible. A few case reports of apparent recovery are hard to interpret, since it is hard to exclude the possibility of unreliable earlier visual field assessments or the subjects learning better to perform the tests [174, 175]. Onset of symptoms has been described to occur from one month to several years after start of treatment [176, 177]. In many cases, there is a distinctive pattern of concentric visual field loss, with relative sparing of the temporal fields and more marked involvement of the nasal fields [171]. This pattern means that even relatively severe concentric losses may be asymptomatic. However, such visual losses have important effects upon lifestyle, the most obvious of which is eligibility for a driving licence.

Cases of visual field loss attributable to vigabatrin have been described in children [178, 179, 180]. These visual losses are particularly evident with static perimetry, but are thought not to be reliably assessable in children whose developmental age is less than nine years [181]. Thus, there is much uncertainty about risks of visual field loss in children treated for infantile spasms.

1.12 Studies comparing ACTH, corticosteroids, or vigabatrin

Placebo controlled trial designs are unusual in treatment studies of epilepsy. It is more common for comparisons to be made between treatments. This section summarises significant studies that compared any two of the treatments studied in UKISS.

1.12.1 Studies comparing ACTH with corticosteroids

Baram *et al* compared treatment with ACTH 150 IU/m^2/day and prednisone 2 mg/kg/day in a randomised trail that enrolled 29/34 eligible infants and recorded response after 14 days of treatment [182]. Hrachovy *et al* reported prospective, open studies of treatment with ACTH and with prednisone, and a randomised, double-blind, placebo-controlled trial. The open studies suggested that cessation of spasms is more likely with ACTH. The Hrachovy group also performed a randomised trial using either ACTH 20 to 30 IU/day or prednisone 2 mg/kg/day, but did not show any significant differences is main outcome [93]. However, the study included only 24 participants. Snead *et al* reported a study comparing treatment of infantile spasms and other childhood seizure disorders with ACTH or prednisone [183, 184]. This study did not have randomly allocated treatments or blinding, and the *seizure control* outcome was not clearly defined. It compared ACTH gel against prednisone with the following regimens. ACTH was given as 150 IU/m^2/day in 2 divided doses for 1 week, followed by 75 IU/m^2/day for 1 week then alternate days for 2 weeks, then a tapering dose over 8 weeks. Prednisone was given as 3 mg/kg/day in 2 divided doses for 4 weeks, then 3 mg/kg/day alternate days for 4 weeks, and was then tapered over a period of 8 weeks. Although these studies influenced

the design of UKISS, the findings of these studies are discussed in more detail in section 6.2.3.

1.12.2 Studies comparing hormonal treatments against vigabatrin

One study has compared hydrocortisone with vigabatrin as first-line treatment of infantile spasms in children whose underlying cause was tuberous sclerosis [16]. Twenty-two participants were randomly allocated treatment, eleven each to hydrocortisone and vigabatrin. The main outcome measure was cessation of spasms during the first month of treatment combined with absence of evidence of spasms on a standard EEG. Absence of hypsarrhythmia was not required to define a primary outcome. Nine (41%) of the children had evidence of hypsarrhythmia on the initial EEG. Only one child was reported to have hypsarrhythmia on an EEG performed at two months after study entry. That child had been treated with both hydrocortisone and vigabatrin, and had not had hypsarrhythmia on the initial EEG.

Information about spasm frequency was obtained from a diary completed by the child's carers, but the paper does not report the minimum period of spasm-freedom that was required in order to define a primary response. All eleven children who were treated initially with vigabatrin were spasm-free at one month, with a reported mean time to cessation of spasms of 3.5 days. Of the 11 children in the group treated initially with hydrocortisone, 5 were spasm-free at one month, with a reported mean time to cessation of spasms of 13 days. The six children who did not respond, and one child that did respond but who had developed an adverse effect, were later treated with vigabatrin, and all of these were reported to be spasm-free at the end of two months. Adverse effects were described in 9/11 participants initially treated with hy-

drocortisone, and in 3/11 of those initially treated with vigabatrin. Some adverse events were classified as "severe", but no distinction was made between serious and non-serious adverse events. One or more adverse effects were reported more commonly in the group allocated hydrocortisone (two-sided Fisher exact test $P = 0.03$). The abstract of the paper quotes an inappropriate P value for the difference in proportions of cases with one or more reported adverse effects. An appropriate statistical test for this difference is the two-sided Fisher exact test.

Only one randomised trial to date has directly compared treatment of infantile spasms with either ACTH or vigabatrin [185, 186, 187]. Forty-two participants were randomly allocated treatment with either 10 IU/day (100 μg per day) of an ACTH depot preparation or vigabatrin 100 to 150 mg/day. If there was an inadequate response to the randomly allocated treatment after 20 days, the alternative treatment was given. The proportion of children whose spasms had stopped before 20 days was 14/19 (74%) in the ACTH-treated group and 11/23 (48%) in the vigabatrin-treated group. The difference in treatment effect, analysed by intention-to-treat, was 26%, with a 95% confidence interval for that difference from -3% to 54% [188]. Data from this study suggest that, for the outcome measure *cessation of spasms*, vigabatrin is unlikely to be a better treatment than low-dose ACTH.

Adverse effects were reported more frequently in the group treated initially with ACTH 7/19 (37%) than in the group treated initially with vigabatrin 3/13 (13%). Typical adverse effects attributed to vigabatrin were drowsiness, irritability and hypotonia; and, for ACTH, hypertension. However, it is difficult to interpret the adverse effects attributed to ACTH because hypertension is not defined in the paper. None of the adverse effects were classified as serious. The authors concluded that vigabatrin is a reasonable first-choice treatment for infantile spasms, the assumption being that it has a lower risk of adverse events

than hormonal treatments.

1.12.3 Hormonal and vigabatrin combination therapy

Zafeiriou *et al* reported combination treatment of 9 infants with infantile spasms, hypsarrhythmia and developmental delay, and who were later found to have cerebral palsy ("static encephalopathy") [189]. The treatment regimen was ACTH 4 IU/kg/day with tapering after 2 weeks and duration of treatment 4 to 6 weeks, and vigabatrin 80–120 mg/kg/day during that same period and continued after ACTH was stopped. Spasms stopped within 7 days in all 9 infants. One child had generalised tonic-clonic seizures 9 months later, and the other 8 were seizure-free after a mean duration of follow-up of 19 months.

Studies such as that of Vigevano and Cilio, and UKISS, in which the alternative treatment is given if the initial treatment is unsuccessful, might be regarded to involve combination treatments rather than crossover treatments, since there is no effective washout period between administration of the initial and subsequent drugs. However, statistical analysis and interpretation of the 'crossover' component of these trials is difficult. For example, only non-responders are given the second treatment, and their outcomes in the second phase of the study cannot be properly regarded as independent of outcomes in the first phase. On the other hand, even though children who fail to respond to the initial treatment may have spasms that are harder to control, there is a natural reduction in time to cessation of spasms that may be modelled as survival time data.

1.13 Aims of this thesis

From the late 1950s until the 1990s, the most popular first-line treatments for infantile spasms were hormonal treatments such as corticotrophin and pred-

nisolone. During the 1990s, vigabatrin became an increasingly popular first-line treatment. However, studies of potential adverse visual field losses, the first cases of which were reported in 1997, suggest that this is a substantial risk, and better estimates of effectiveness and risks associated with these treatments are now essential.

The initial aims of this thesis were to provide epidemiological information about the incidence of infantile spasms in the United Kingdom, and to report the results of a randomised controlled trial of three treatments for this serious condition. The main instrument for meeting these aims was the United Kingdom Infantile Spasms Study (UKISS). Slow accrual of cases and emerging issues about potential designs for studies of infantile spasms led to a change in emphasis and aims for this thesis. It was evident that there is a need for standardisation for case definitions and outcome measures in studies of infantile spasms, and presentation of provisional ideas on this theme led to a consensus elicitation process called *West Delphi*.

Chapter 2

The United Kingdom Infantile Spasm Study Design and Protocol

2.1 Early development of UKISS

2.1.1 Origins of the study

The United Kingdom Infantile Spasm study originated in discussions in 1995 between Professor John P. Osborne, Dr Eleanor Hancock and Dr Finbar J.K. O'Callaghan. At that time vigabatrin was becoming increasingly popular as a first-line treatment for infantile spasms, but these discussants were not convinced that vigabatrin had proven itself to be better than hormonal treatments. Professor Osborne had experienced success in treating infantile spasms with doses of oral steroids that are higher than those usually used. A retrospective study of cases of infantile spasms that had been treated with prednisolone, an oral corticosteroid, at the Royal United Hospital, Bath showed that prednisolone had a good treatment effect and that few important adverse effects were observed [162].

These investigators suggested two questions. First, are hormonal treatments or vigabatrin significantly better first-line treatments of infantile spasms

than the other? And second, is the apparently better treatment effect of ACTH that has been reported in some studies due to an insufficient dose or duration of oral corticosteroids? These questions were discussed with paediatric neurologists in Cambridge, Liverpool, London, Manchester, and Southampton, and a statistician at the Medical Research Council Biostatistics Unit in Cambridge. These formed a core group that later developed into the UKISS trial steering committee (appendix A).

Applications for funding for the study were made first to the Medical Research Council (MRC), with an initial proposal submitted in June 1996. The response to this proposal was made in November 1996 and stated that the study was potentially competitive. A full proposal was submitted in February 1997, but the final decision was that the study would not receive MRC funding. A proposal for funding was then made to the Bath Unit for Research in Paediatrics (BURP), which agreed to fund the application with a grant to be held at the University of Bath.

2.1.2 Rationale for the study

The rationale of the United Kingdom Infantile Spasm Study was to obtain reliable estimates of treatment and adverse effects of hormonal and vigabatrin treatments of infantile spasms in order to decide if any one of them can be regarded as the best first-line treatment. It was considered important that prednisolone and tetracosactide were administered with regimens that were similar in duration and potency. Part of the rationale for the study was to use reliable neurodevelopmental outcome measures, since these are arguably more important outcome measures than cessation of spasms and resolution of EEG features.

2.1.3 General form of the study

A major aim of the study was to place these effect measures in the context of the public health importance of infantile spasms. Though small in number and influenced by underlying causes, there is a substantial cost burden for morbidity due to infantile spasms. Thus, the study aimed to get reliable estimates of incidence rates and, even though the absolute numbers are relatively small, the study was intended to be in the form of an effectiveness study rather than that of an efficacy study. The analysis of data from participants who were prospectively and contemporaneously enrolled in the non-randomised study is broadly consistent with the approach of an effectiveness study. The findings from this element of the study are not presented in this thesis.

Efficacy studies aim to measure treatment and adverse effects due to treatments or other interventions, making measurements that attempt to control for extraneous occurrences such as non-compliance with treatment and misclassification of either diagnosis or outcome. In general, such studies are used to make inferences about biological effects. They tend to be small studies with relatively homogeneous participants [190].

Effectiveness studies aim to look at the effects of interventions applied on a large scale. Such studies are used to assess the impact of an intervention or treatment on larger populations, employing simple methods of assessment and data capture. They address the question of what effect the intervention would have on a population where non-compliance, heterogeneity and misclassification will occur and might be common. Synonyms include *effectiveness trials, public health trials, large-scale* and *large simple* (LS) trials.

Effectiveness trials have several advantages. Treatments based on sound biological principles may be less effective when used outside the setting of a homogeneous population in a highly controlled trial. Effectiveness trials have

greater external validity and are likely to have a faster impact on clinical practice. However, in most therapeutic areas, effectiveness trials would enroll large numbers of participants, and possibly tens of thousands.

2.2 Classification of infantile spasms used in UKISS

The most inclusive definition of infantile spasms requires the characteristic clinical feature, the spasms, but does not require any specific age limit or the presence of any particular EEG feature [28]. Earlier classifications of infantile spasms into *symptomatic* and, variously defined, *cryptogenic* or *idiopathic*, groups has been followed by the definition of a more specific idiopathic group. However, the distinctiveness of this idiopathic form of infantile spasms has not been generally accepted, and some investigators have suggested that this classification also will change in the future [36].

In keeping with the pragmatic criteria of an effectiveness study, the study protocol of the United Kingdom Infantile Spasm Study used the clinical diagnosis of the local investigator to define a diagnosis of infantile spasms, and did not state highly specific clinical and electroencephalographic criteria (appendix B.1). The study used cessation of seizures as measured by the carers and local investigators as measures of outcome. As such, it measures the effects of treatment of infantile spasms as diagnosed and assessed using criteria that were in common practice in the UK at the time of study design.

In UKISS, we used the term *symptomatic* as outlined in earlier definitions, and we include neurodevelopmental delay identified before onset of spasms as a risk factor for symptomatic onset. We consider the cryptogenic and idiopathic forms of infantile spasms to be distinct, although not necessarily distinguishable, and we refer to these forms collectively as *non-symptomatic*. These definitions allow inclusion of children who have the clinical features of in-

fantile spasms, irrespective of whether the EEG shows features described as hypsarrhythmia. It was expected that local investigators would perform sleep or video EEGs if standard EEGs are normal, since these more sensitively detect abnormal EEG patterns. Children with normal awake and sleep EEGs are considered to have a form of benign myoclonus, since a normal EEG pattern is considered to be incompatible with a diagnosis of infantile spasms.

At the time of study enrolment, cases were classified as being at risk of having symptomatic infantile spasms, or as being likely to have non-symptomatic infantile spasms. Unless otherwise stated in this thesis, this classification – made at the time of diagnosis of infantile spasms – rather than any classification made later and after further investigation, is used for subgroup analyses based on aetiology. Subgroup analyses of outcomes based upon this initial aetiological classification will best inform initial treatment decisions. Where analyses are based on classifications based on later or final diagnoses, we clearly state that a secondary classification is being used.

2.3 Issues relating to the UKISS study protocol

The protocol of the United Kingdom Infantile Spasm Study is reproduced in appendix B.1. Some elements of the study protocol required further definition and development, as discussed in the following sections.

2.3.1 Eligibility criteria

Section four of the study protocol suggests that an EEG should be performed soon after a clinical diagnosis so that treatment should not be delayed for more than 72 hours. The trial steering committee considered it important, for ethical reasons, that treatment decisions should not be delayed for longer than this period. One scenario that was not considered in the study protocol is that in

which a local investigator considers infantile spasms as part of a differential diagnosis but wishes to defer treatment until an EEG has been performed and supports the diagnosis. In such cases, there is not any issue of treatment delay attributable to participation in the study, since the delay is attributable to working practices in that district. We considered this scenario in the context of the study aims and decided that such cases should be eligible to enroll if the treatment was decided within 72 hours of the local investigator interpreting the EEG and diagnosing infantile spasms.

2.3.2 Exclusion of cases with tuberous sclerosis

The UKISS trial steering committee considered at the early design stage of UKISS that there was a strong, though not unanimous, opinion amongst paediatricians and paediatric neurologists in the United Kingdom that infantile spasms occurring in infants who have tuberous sclerosis respond particularly well to treatment with vigabatrin. It was thought that, since most treating physicians were likely to prefer vigabatrin over hormonal treatments in such cases, there would be relatively small numbers of cases with tuberous sclerosis allocated to each of the randomisation strata. It was felt that this would make the interpretation of outcomes in the tuberous sclerosis group difficult, and that it would be better to exclude these infants from the randomised controlled trial (section B.1 on page 245). However, it was intended that they would be included in the non-randomised element of the study. This is discussed further in section 6.2.12.

2.3.3 Outcomes

Issues relating to outcome are detailed in sections 14-19, 21, 25, and 26 of the study protocol (appendix B.1, pages 249 to 251). The structure of data used to

measure outcomes was not fully defined by the study protocol and was developed further as the the main tools for obtaining these data were developed. These tools were the patient's diary and the trial folder.

Response and relapse: Definitions for these are given in section 14 of study protocol (page 249). The study protocol states that a responder is a child "in whom there is total cessation of spasms for at least 48 hours up to and including the end of the fourteenth day of treatment." This definition, taken alone, is ambiguous. One interpretation requires that cessation occurs before the end of the 12th day, and a spasm-free period of at least 48 hours, but would permit relapse to occur before the end of the 14th day. A second interpretation requires that the spasm-free period include the end of the 14th day, and would not permit relapse to occur before that time. The UKISS Trial Steering Committee agreed that the primary outcome would be determined using the definition that required cessation of spasms to include the end of Day 14 after allocation of randomised treatment, and Professor Osborne confirmed that this was his initial intention behind the definition.

Relapse: A relapse is defined as *a single spasm in a responder*. Two observations are pertinent. First, the intended definition would be more precise if it read *one or more spasms*, since there would be no plausible reason to require a spasm to be single rather than part of a cluster in order for it to constitute a relapse. Second, it could be argued that relapse presupposes response and that, since the third paragraph of section 14 discusses the scenario in which a child relapses before the end of the fourteenth day, we may deduce that both relapse and response may occur before the end of the fourteenth day. However, the trial steering committee discussed this issue and confirmed that the term *relapse* was used in the looser sense of "recurrence of spasms" rather than

indicating "recurrence of spasms after a primary clinical outcome". Hence, the first interpretation stated in the above section remains appropriate and was the definition intended by the trial steering committee. In other words, for the primary outcome to be considered positive, cessation of spasms had to occur before the end of study day 12, with no reported spasms throughout study days 13 and 14.

Main outcome: The definition of the primary outcome measure given in section 25 of the protocol (page 251) is ambiguous in the same way as the definition of a responder. However, it is clear from the above discussion that its intended definition is as discussed in the two sections above. The actual main measures of effect are proportions derived from the numbers responding to each allocated trial treatment.

Secondary outcomes

Some of the secondary outcome measures stated in Section 26 of the study protocol (page 251) required further details for clear definition.

Time to cessation of spasms: The time taken to cessation of spasms (subsection 26.1) is that period between allocation of randomised treatment (Day 0) and the first spasm-free day that heralded a period of 48 hours or more of freedom from spasms.

Resolution of hypsarrhythmia at Day 14: *Resolution of hypsarrhythmia at Day 14* (subsection 26.5) is only measured in children who had hypsarrhythmia at enrolment and whose spasms have ceased, consistent with a primary clinical response.

Normalisation of EEG pattern: This is another potential outcome measure used in children who are primary responders, and refers to finding an EEG pattern that is within normal limits in cases where there was any EEG abnormality, either hypsarrhythmic or non-hypsarrhythmic, at the start of the study. However, this outcome is less useful than *resolution of hypsarrhythmia* because it is more strongly influenced by underlying disorders and would not necessarily be expected to occur even if the infantile spasms were successfully treated.

Partial response: The reduction in number of spasms required to define a partial response (section 26.2) is to 50% or less of the original number of clusters of spasms.

Relapse rates: The *relapse* outcome of most interest is the proportion of infants responding and relapsing by the end of the study. This can be represented as the proportion of randomised participants responding and relapsing, or as the proportion of respondents that later relapse. The former representation is preferable because it presents the data with the randomised unit as the denominator.

2.3.4 Patient Diary

The development of the diary was an important extension of the study protocol. Its structure and content had to balance several competing demands. First, the questions asked had to give information relevant to the outcomes sought by the study. Second, the diary had to be simple enough for use by carers with modest reading ages and who were not familiar with medical terms. Third, it required a balance between seeking quantitative data and not encouraging carers to report with spurious accuracy.

We required that treatment of infantile spasms not be delayed by the ad-

ministration of the trial. For this reason, it was not possible to have a prospective period of data collection before treatment started. The ranges for counts of spasms during the week before treatment started were as follows. For the number of clusters per day: 5 or fewer; 6 to 10; 11 to 20; 21 to 40; more than 40. For the number of spasms in a cluster: 5 or fewer; 6 to 10; 11 to 20; 21 to 40; 41 to 80; more than 80. However, it was later considered, particularly in the light of comments from participants in West Delphi, that the *partial response* outcome discussed above is of little value and it was later decided not to analyse these data.

2.3.5 Classification and reporting of adverse events

Classification of adverse events

Section 18 of the study protocol (page 250) stated that the trial centre should be informed and treatment should be stopped if there were unacceptable adverse effects. This section was considered by the data monitoring and ethics committee not to define adequately serious adverse events. This was reviewed by the trial steering committee. There were several issues.

First, it might be desirable to continue treatment with prednisolone or tetracosactide if an adverse event was caused by adrenocortical insufficiency. Such insufficiency might be due to inhibition of central stimulation of the adrenal cortex and would be best treated by continuing or increasing the dose of prednisolone or tetracosactide. Thus, it was inappropriate to recommend that the treatment should be stopped in all cases where there had been a reported adverse event, and it was inappropriate to use the need to stop treatment as the sole criterion of seriousness.

There was a second issue relating to stopping treatment as the sole criterion of seriousness. Even though the duration of treatment with vigabatrin is left to

the discretion of the local investigator, the duration of exposure to vigabatrin is likely to be longer than that of exposure to prednisolone or tetracosactide. In addition, adverse events due to prednisolone or tetracosactide might occur after treatment had stopped. Thus, there might be an important bias such that, using the stopping of treatment criterion, serious adverse events would have a greater chance of being recorded in participants receiving vigabatrin since the duration of treatment with that drug is longer.

A third issue was that of classifying any adverse events. The steering committee considered developing the protocol to code adverse events according to the *Medical Dictionary for Regulatory Activities (MedDRA)*. MedDRA is a standard medical terminology for drug regulation that has its origins development of standard terms for the *Adverse Drug Reactions On-line Information and Tracking (ADROIT)* database of the UK *Medicines Control Agency (MCA)* [191]. This terminology was adopted by the International Conference on Harmonisation (ICH) in October 1994, under the name *Medical Dictionary for Drug Regulatory Affairs (MEDDRA)*. MedDRA is an "implementable version" of MEDDRA, and was adopted by the ICH in July 1997. However, it was decided that, although we wished UKISS to conform to ICH recommendations and standards as much as possible, the cost and complexity of MedDRA was inappropriate for a study with the budget and resources of UKISS.

Duration of monitoring

Information about adverse events was sought from both the local investigator and the carer throughout the study, from the diary, day 14 report form, forms submitted at 3-monthly periods after enrolment, and at the time of final follow-up. Serious adverse events were reported to the local and multicentre research ethics committees (LREC and MREC) and the data monitoring and ethics committee (DMEC) during the course of the study. Using agreed cri-

teria, we reported any deaths in study participants during the study period, admissions to hospital that were potentially attributable to an adverse effect of medication, withdrawal of medication due to a treatment adverse effect, and cases where extra treatments were required because of medication.

Reporting of adverse events

It was considered important to obtain complete information about potential adverse reactions. The questions about adverse events were left open-ended and invited responses about unusual reactions, other illnesses and other treatments. They did not require the local investigator to consider the event to be directly attributable to the treatment (that is, an *adverse reaction*) but encourage reporting of any adverse event. This wide range of questions was chosen to increase the sensitivity and completeness of reporting, and provided information that would allow later consideration of whether the treatment was directly related to the adverse event. Closed questions about specific, expected drug reactions were not asked, since we thought that they would be suggestive and prompt responses.

The table in the patient's diary that seeks information about continuing seizures asks about seizures during the week after the participant's first birthday. This was chosen because it was memorable and would be measured at a standard age. The table provides information that can be compared with the local investigator's reporting of continuing seizures at the time of the final assessment. Participants enrolled at less than 9 months of age would have a final assessment at 12 months of age. However, those enrolled at nine months of age or greater could have a final assessment up to the age of 14 months, and reporting of continuing seizures by the local investigator and in the patient's diary, since they refer to different ages, might be different.

2.3.6 Definition of treatment days

The timing of follow-up consultations and investigations was stated in the study protocol (section 14, page 249) but the definition of study days was not explicitly stated. We decided to classify the day on which a treatment decision was made as *Day 0*. This was likely to be the same day as the day of notification and, for participants enrolled in the randomised trial, the day on which randomised treatment was allocated. All subsequent days start at midnight because a fixed time for increments to occur is simpler than one that varies between participants. Also, this is consistent with the timing of reported spasms obtained from the patient's diary. Thus, *Day 0* was of variable length and it is possible, where treatment was allocated late in day, that the first dose of treatment would be given on *Day 1*, even though in fact given within several hours of treatment allocation.

2.3.7 Timing of the follow-up EEG

An important consideration was the timing of the follow-up EEG. The protocol requested that this be performed soon after day 14 of treatment but not before that day (section 26.5 of study protocol). There were two issues with this requirement. First, local investigators might request an EEG at a time that would make it available for review by them at the day 14 visit. We thought that this would be convenient for the participant and carers and ought not to be considered as a protocol violation. Second, a primary outcome would require the last seizure to have occurred before the end of day 12, and resolution of EEG abnormalities is an outcome of interest only in participants who have become spasm-free. For these reasons, EEGs measured between day 12 and day 14 are likely to provide important information and ought not to be classified as protocol violations. In order to allow follow-up EEGs to be performed later than

14 days without serious bias occurring, we decided that EEGs performed after day 14 but before day 20 would be included as valid outcome investigations. Thus, the timing of valid follow-up EEGs was any time during a full week from the time cessation of spasms had to have occurred to five days after the timing of the follow-up assessment.

2.4 Study treatments

2.4.1 Prednesol®; prednisolone

Glaxo Wellcome, Stockley Park West, Middlesex, UB11 1BT. Small tablets; pink; engraved *Prednesol Glaxo* on one side and scored on the reverse. Each tablet contains 5 mg of prednisolone as the sodium phosphate ester. After a change of licence, most centres used prednisolone soluble tablets, Sovereign Medical, Sovereign House, Miles Gray Road, Basildon, Essex, SS14 3FR, UK.

2.4.2 Synacthen® Depot; tetracosactide

The former BAN for this drug was tetracosactrin and the rINN is tetracosactide. Alliance Pharmaceuticals UK Ltd, Avonbridge House, 2 Bath Road, Chippenham, Wiltshire, SN15 2BB. A sterile, white suspension that settles on standing. Contains 1 mg of Synacthen per ml and 10 mg of benzyl alcohol per ml. The preparation is available in 1 ml ampoules, which also contain zinc, sodium phosphate, sodium chloride, sodium hydroxide, and water.

2.4.3 Sabril® Sachets; vigabatrin

Hoechst Marion Roussel Ltd, Broadwater Park, Denham, Uxbridge, Middlesex, UB9 5HP. From March 2000, when there was a merger and reorganisation, the manufacturer of Sabril was Aventis Pharma Ltd, Aventis House, 50 Kings

Hill Avenue, West Malling, Kent, ME19 4AH. Sachet of powder containing 500 mg of vigabatrin.

2.4.4 Treatment allocation

Randomised treatment was allocated by opening sealed envelopes that had been prepared by Dr Peter Lewis, a biostatistician in the Department of Medical Sciences of the University of Bath. Sixteen randomisation blocks were used to reduce the chances of important differences in potential prognostic factors between randomised groups. These factors were: sex; symptomatic or non-symptomatic status at onset; and four age categories. These are outlined in the study protocol.

2.4.5 Concomitant therapy

Concomitant treatments were allowed. In particular, participants who were being treated with antiepileptic drugs at the time of enrolment were allowed to continue such treatments if that was the local investigator's preference. The study protocol allowed but discouraged starting pyridoxine during the first 28 days of the study.

2.4.6 Permitted modifications and protocol violations

The study protocol did not define limits outside of which an action would be considered to be a violation of the protocol. For more important features of the study, such as the timing of valid follow-up EEGs and tolerance limits for the timing and dosing of trial treatments, such limits were defined and applied prior to data analysis.

The treatment schedule is described in the section 8 of the study protocol (page 246) and compliance is discussed in section 21 (page 250). These did not

specify explicit criteria defining compliance with treatment intervention, but such criteria were defined by the trial steering committee before data analysis. Rounding doses of vigabatrin, which was dependent upon the weight of the child, was permitted. Treatments were considered non-compliant if any changes in dose or schedule occurred outside a 24-hour limit of that stated in the study protocol, and any treatment dose was considered non-compliant if it fell outside a 10% limit of the dose stated in the protocol.

2.4.7 Consent procedures

Informed consent was obtained from the carer after counselling by a local investigator and completion of a consent checklist. The checklist ensured that essential information and rights were communicated to the carer. A copy of the signed consent form was given to the carer for future reference. Comments from LRECs and new information about the risks of visual field loss associated with vigabatrin were incorporated into two new information sheets that were given to parents or guardians before consent was sought. These *Extra information sheets for parents or guardians* were approved by the MREC and constituted protocol amendments dated 11 May 2000 and 30 April 2001. Relevant information from these information sheets is shown on pages 252 and 254.

2.4.8 Masking

No masking, or blinding, was employed for several reasons. First, providing placebo preparations of injectable drugs would almost certainly have been regarded as unethical and would have discouraged participation in the study. Second, there would have been added costs in obtaining and distributing placebo medications. Third, the role of the local pharmacy would have been more important, and this would also have added substantially to the cost and ad-

ministrative demands of the study. Finally, it would have been difficult to maintain an effective blinding if there were prominent identifiable adverse effects of one of the treatments, such as increased appetite and weight gain with hormonal treatments.

2.4.9 Conduct of study after assessment of primary clinical outcome

Following the assessment on study day 14 of the study, the infants were reviewed by the local investigator as often as was deemed necessary. The protocol requested 3-monthly reports that included information on any spasms since the last assessment, any other epileptic seizures, changes to treatment, adverse events, and details of further investigations. A final clinical assessment was made by the local investigator when the enrolled infant was approximately 12 months old.

After reporting the early outcomes, the parents or guardians were asked to complete a diary daily between study days 15 and 28, and thereafter to complete these details weekly. Diary information included the occurrence and number of any spasms, and adverse events. In addition, on a daily basis during the last week before their final assessment, the parents were asked to record any spasms or epileptic seizures.

Infants who had not responded to their allocated treatment by day 14 were given treatment determined by their local investigator. The protocol requested, but did not require, that the local investigator offer the alternative trial treatment (vigabatrin after hormonal treatment and vice versa) at the trial dosage. If an infant who had responded to vigabatrin then relapsed, we suggested that the local investigator increase the dose to around 150 mg/kg. In the case of relapse in an infant who had responded to a hormonal treatment, the protocol

suggested repeating the course of hormonal treatment once before offering the alternate treatment.

The three monthly reports, final report, diaries and any other information sent such as copy clinic letters, were scrutinised by two members of the trial steering committee, Professor John P. Osborne and Dr Stuart W. Edwards. They independently looked for any evidence of relapse, defined as any episode of recurrent spasms, including even a single reported spasm. Later clinical response was defined, as for the primary clinical response, as a period of 48 hours with no reported spasms. In addition, these reports recorded any period of greater than one month in which there was absence of clinical evidence of spasms.

2.4.10 Developmental assessment

Developmental assessments were made around the age of 14 months using *Vineland Adaptive Behavior Scales: Interview Edition, Survey Form* (VABS) [192]. This is similar in content to the original Vineland and provides a general overview of adaptive behavior using 297 items. There is also an *Interview Edition, Expanded Form* with 577 items that include the 297 items from the survey form. The expanded form is suitable for assessment of individual treatment programmes and specific educational needs, but the survey form is suitable for comparisons of groups.

The Vineland scales cover a range of adaptive behaviours in four domains, each of which have two or three subdomains (shown in parentheses): communication (receptive, expressive, and written); daily living skills (personal, domestic, and community); socialization (interpersonal relationships; play and leisure time; and coping skills); and motor skills (gross and fine). An adaptive behaviour composite score is derived by summing the scores from these domains and applying an adjustment for age at time of assessment. This score

was used as the primary neurodevelopmental outcome for UKISS and is hereafter referred to as the *Vineland ABC score.*

The Vineland test has been standardized on a sample of 3000 children forming a representative national sample matched to United States census data. The sample was stratified by age, race, gender, region, parental education, and community size, and additional interpretative data were obtained from supplementary norm groups of children with disabilities. It has been been used in the United Kingdom for other developmental follow-up studies, and in the United States for developmental studies on children with infantile spasms [193, 194]. The age adjustments are applied by monthly age periods, and the standardised score has a population mean of 100 points and a standard deviation of 15 points.

Vineland assessments were made by the author, who acted as the sole assessor, performing a telephone interview of one parent or guardian. The assessor refrained from examining the records of each child before making the telephone call and asked the parent or guardian not to make any specific comments about treatments until after the Vineland assessment was complete, but he was not blind to allocated treatment. No estimate of sample size was undertaken for this part of the study since there were no reliable prior data on which to estimate effect size.

2.5 Data and safety monitoring

A data monitoring and ethics committee was invited to review the study. The members of this committee are listed in Appendix A. There was no set date for trial termination other than recruitment of 250 trial participants. It became evident after only six months of the study that enrolling 250 trial participants would take far longer than had been anticipated.

Any decision to recommend early termination of the study was at the discretion of the Data Monitoring and Ethics Committee. The priority was the safety of the enrolled infants. However, there was no predetermined number or proportion of adverse events of any kind that would be considered sufficiently important to recommend trial termination. In addition, since outcomes determined at 12 to 14 months of age were at least as important as earlier outcomes and would be relatively statistically underpowered if the study were terminated early, a significant difference in the earlier outcomes would not necessarily lead to a recommendation that the trial be terminated early.

2.6 Safety, licensing, and ethical issues

2.6.1 Licensing provisions for treatments used in UKISS

Synacthen Depot is not licensed for marketing as a treatment of infantile spasms. Local investigators using Synacthen Depot on participants of UKISS were exempted from the need to have a clinical trial certificate (CTX) under the Doctors' and Dentists' Exemption Scheme (DDX) outlined in The Medicines (Exemption from Licences)(Special Cases and Miscellaneous Provisions) Order 1972. The MCA makes such exemptions when it has not positively assessed the product for safety, quality or efficacy. The DDX approval for Synacthen® Depot was effective from 10 September 1998. The MCA also granted a DDX approval for the use of Prednesol®, which also had no licence for specific use as a treatment for infantile spasms.

For vigabatrin (Sabril®), the summary of product characteristics states that monotherapy of infantile spasms is a specific indication for use, and so no special licensing arrangements were required. This specific indication remained after the extensive review by the *European Committee on Proprietary Medicinal*

Products.

2.6.2 Withdrawal of licence for ACTH

The first UKISS study design was intended to compare vigabatrin with prednisolone and ACTH. However, there had been increasing concern and uncertainty at that time about the risks associated with using bovine products because of uncertainty about risks of new variant Creutzfeld-Jakob disease (nvCJD), and the trial steering committee had already considered suitable alternative products. ACTH was withdrawn from the UK market in 1997 but is in fact derived from porcine brains. Synthetic forms of ACTH have been used since the 1960s, and these are a natural choice as an alternative to bovine-derived ACTH.

2.6.3 Visual field losses associated with vigabatrin

The first reports of visual field losses in patients being treated with vigabatrin appeared in 1997. A causal link was considered, but the problem was not thought to be important. First, the risk was thought to be low. Second, the drug had been marketed for seven years before these first cases were reported. And third, the adult cases that were first reported had been asymptomatic and the visual field losses had not interfered with their lifestyle until the diagnosis was made.

The potential risk to visual fields due to treatment with vigabatrin was notified to the MREC in May 1998. At this time, Hoechst Marion Roussel regarded the small number of reports as important and undertook to provide the study with periodic safety update reports (PSURs).

As a result of prospective studies, it is thought that there occurs a specific form of visual field loss, known as vigabatrin-attributable visual field loss (V-

AVFL). This is typically concentric and more marked in the nasal quadrant of the visual field. The severity of these visual field losses can be classified according to a guideline that uses kinetic perimetry with a 14e isopter reference and angles subtended in the temporal, superior, nasal, and inferior visual fields. Severe losses are defined as those associated with angles of vision less than 30 degrees in all quadrants, and less than 20 degrees in the superior and nasal quadrants. Moderate losses are associated with angles less than 50 degrees in all quadrants, and less than 35 degrees in the superior and nasal quadrants. Mild losses are associated with angles less than: 70 degrees in the temporal quadrant; 50 degrees in the inferior quadrant; 45 degrees in the nasal quadrant; and 40 degrees in the superior quadrant.

Although patients who have these visual field losses generally have no related symptoms, the losses are sufficient to require that a driving licence be withdrawn. In the light of these new risks, there was a major review of vigabatrin by the European *Committee for Proprietary Medicinal Products (CPMP)*. New prescribing information was issued by *Hoechst Marion Roussel* in August 1999, and monotherapy of infantile spasms remained a specific indication for use. At that time, visual field losses had not been reported in children.

2.6.4 Tetracosactide and benzyl alcohol

On 12 June 1997, the *Pharmaceutical Committee of the European Commission Directorate-General III, Industry, Industrial Affairs III (DGIII/E/3)* issued a guideline that acts as an annex to the European Union Council Directive 75/318/EEC. This *Guideline on the Excipients in the Label and Package Leaflet of Medicinal Products for Human Use* is now included in *The Rules Governing Medicinal Products in the European Community Volume IIIB: Guidelines*. It states that the label of products intended for parenteral use and which contain benzyl alcohol as an excipient should state: *Contraindicated in infants or young children; up to 3 years*

old. Samples of the outer and immediate packaging and of the package leaflet have to be submitted to the competent authority before the product may be used commercially. Package leaflets were formerly known as *datasheets*, but were subsequently referred to as a *Summaries of Product Characteristics (SmPCs)*.

On 3 March 1999, the Medicines Control Agency endorsed the new SmPC for Synacthen® Depot, and this included the statement that the product is not recommended for use in children under 3 years old. The Medical Assessor at the Clinical Trials Unit of the MCA was unable to establish or obtain the pertinent data used to justify the guideline. A request for this information was also made to the Head of Unit at DGIII/E/3, but we did not receive a response. A review of published papers about benzyl alcohol suggested a small number of papers which might have influenced the EU guideline. We summarised the findings of these papers and submitted the summary and original papers to the MREC.

Gershanik *et al* reported a syndrome of respiratory distress, convulsions, metabolic acidosis, and sometimes death, in children associated with administration of benzyl alcohol with estimated doses of 99 to 234 mg/kg/day. All of these infants had birth weights less than 2.5 kg [195].

Anderson *et al* reported the case of a 3.35 kg, 35-week gestation neonate that had high levels of benzoic acid, a liver metabolite of benzyl alcohol, and of hippuric acid, the glycine conjugate of benzoic acid [196]. They estimated that she had received between 32 and 105 mg/kg of benzyl alcohol during the first 7 days of life, the source being a sodium chloride vascular flush that contained benzyl alcohol at a concentration of 9 mg/ml. They suggest that the cause of elevated benzoic acid levels are immature hepatic conjugation and renal excretion, and that the infant they reported was at risk because her liver function was impaired by hydrops fetalis. They were not certain that her respiratory symptoms were attributable to benzyl alcohol.

Hiller *et al* reviewed 198 infants with birth weights less than 1.25 kg in Portland, Oregon [197]. The earlier cohort of 103 infants had received vascular flush solutions containing benzyl alcohol, and the later cohort of 95 infants had received solutions without benzyl alcohol. The later cohort had a lower mortality rate: 35/95 (37%) compared with 64/103 (62%) ($\chi^2_{(1)} = 12.6$, $P < 0.001$). An associated study reported that the earlier cohort also had a higher rate of cerebral palsy [198]. Even though a bias due to period effects is likely and survival might be expected to be better in a later cohort, this appears to be good evidence that benzyl alcohol increases mortality and morbidity in preterm infants.

Jardine & Rogers reported outcomes on 450 infants admitted to neonatal intensive care units in Pittsburgh, Pennsylvania, USA [199]. An earlier cohort of 218 infants had received benzyl alcohol, but a later cohort of 232 infants had not. The earlier cohort had an increased risk of intraventricular haemorrhage of grade II or higher and there was evidence of an inverse dose-response effect for this risk: relative risk was higher in neonates who received less than 30 ml/kg of flush solution than in those who had received more than 30 ml/kg. This apparent inverse dose-response effect is hard to interpret. Kernicterus, yellow staining of the basal ganglia of the brain due to infiltration by bilirubin, was found at postmortem examination in 15/49 (31%) of infants who had received benzyl alcohol during the earlier period, and in none of 22 infants who were examined in the later period and who had not received benzyl alcohol.

In addition to reviewing published data, we asked the United Kingdom *Medicines Control Agency Pharmacovigilance Group* to perform an *ADROIT Database* search on benzyl alcohol. The database search result was reported on 7 April 2000 and showed no reported cases of metabolic acidosis, kernicterus or intraventricular haemorrhage associated with the use of benzyl alcohol in the UK in children outside the immediate neonatal period.

The UKISS trial steering committee informed the MREC of the change in the *Summary of Product Characteristics* and stated its interpretation that there were minimal risks associated with the administration, outside the immediate neonatal period, of the very small amount of benzyl alcohol contained in Synacthen® Depot. The MREC approved the continued use of Synacthen® Depot and no further action was required.

2.6.5 Tetracosactide and anaphylactic reactions

The study protocol was reviewed by the MREC after ACTH was replaced by Synacthen® Depot. The MREC wished to know more about risks of anaphylactic reactions caused by Synacthen® Depot. The UKISS steering committee requested a search of the Medicines Control Agency ADROIT database for serious adverse effects associated with tetracosactide. This search revealed 12 reported cases of fatal or serious reactions in children aged 17 years or under. The youngest of these cases was 2 years old, and this was the sole report in a child under 5 years of age. Two of the reactions were fatal. These occurred in children aged 14 and 15 years of age, and were not necessarily attributable to tetracosactide.

Even though the number of children given tetracosactide during that period is not known, and many cases of adverse effects are not reported to the MCA, the interpretation of the UKISS Steering Committee was that this search suggested a low risk of serious adverse effects due to Synacthen® Depot in infants aged less than 1 year. In general, anaphylactic reactions are rare in young children, and the UKISS steering committee thought that the risk any such reaction during the study was low. The MREC was informed about the results of the ADROIT Database search, and it agreed that tetracosactide could be used in the study.

2.6.6 Indemnity arrangements

Any study sponsored by a member of the *Association of British Pharmaceutical Industries (ABPI)* requires indemnity arrangements that include payment of no-fault compensation. Such arrangements are not required of studies, such as UKISS, that are not sponsored by pharmaceutical companies. The UKISS steering committee considered obtaining such indemnity, and Professor John Osborne told the MREC about these explorations on 6 March 1998. However, arrangements for no-fault compensation payments were not completed because they would have been too expensive.

The *National Health Service Litigation Authority (NHSLA)* confirmed that it undertakes to provide indemnity for NHS personnel participating, as part of their NHS duties, in studies that have appropriate approval from research ethics committees and NHS trusts. However, this indemnity would not extend to members of the UKISS Steering Committee for actions relating to study design and conduct that would not be considered to be part of normal NHS duties.

2.7 Statistical methods

Statistical analyses were made using Stata Release 8.0 [200]. The unit of analysis was the individual participant in the study. All analyses of trial data were made by intention to treat and according to the recommendations of the revised CONSORT statement (Consolidated Standards of Reporting Trials) [201].

2.7.1 Summary and test statistics for main outcomes

The intended primary outcomes for UKISS were the proportions with cessation of spasms for a period of at least 48 hours, and including study days 13

and 14, after allocation of randomised treatment. The intended primary analyses were of hormonal treatments versus vigabatrin, and of prednisolone versus tetracosactide, as described in the UKISS study protocol (appendix B.1). Differences in proportions are compared using Pearson chi-square tests (abbreviated as $\chi^2_{(d)}$ where d indicates the number of degrees of freedom) often with reporting of effect estimates and 95% confidence intervals (CIs). Neurodevelopmental outcomes and other continuous variable data are compared by means of unpaired t-tests. A two-way analysis of variance (ANOVA) model is used to investigate the relative contributions upon neurodevelopmental outcomes of randomised treatment, presence or absence of identified underlying aetiology, and presence or absence of primary clinical response. The comparison of contrasts from the ANOVA model is made using the least significant difference (LSD) test [202]. Kaplan-Meier estimates are used to graphically represent time to reported spasms after study day 14 [203].

2.7.2 Planned multiple tests and subgroup analyses

Subgroup analyses were not clearly defined in the UKISS study protocol, but with respect to neurodevelopmental outcomes there was *a priori* interest in any differences in the subgroup with no identified underlying cause. This was the only subgroup analysis approved *a priori* by the trial steering committee.

2.7.3 Stratification at randomisation to control for potential prognostic factors

With such an uncommon condition and the relatively small sample size, there is a limited number of prognostic factors that can be controlled. Randomisation occurred in groups stratified by sex and by age; and by a composite variable defined by whether there was a diagnosed underlying cause at time

of randomisation or developmental delay that preceded the onset of spasms, or both. These randomisation strata were intended to reduce the chance of significant imbalance between treatment groups, but we were aware that the small numbers would severely limit any formal tests for heterogeneity of effect across strata and formal analysis of prognostic factors. Probably the strongest prognostic factor for response to treatment with vigabatrin, a diagnosis of tuberous sclerosis (TSC), was controlled by making children with this diagnosis ineligible for randomised treatment. However, up to 70% of children with TSC have new mutations and will not be identified by family history, and diagnosis may not occur at the time of allocation of randomised treatment.

Chapter 3

Study Conduct and Early Outcomes from the United Kingdom Infantile Spasms Study

This chapter presents analyses of UKISS data. Section 3.1 describes the progress of the study and shows that the accrual of participants was substantially slower than had been predicted by the trial steering committee. Section 3.2.1 describes a study of response times by local research ethics committees, the results of which were published in the *BMJ* [204]. Section 3.3 describes baseline characteristics of study participants, in particular underlying aetiology, and information relating to compliance. Section 3.4 describes findings relating to the primary clinical response, cessation of spasms, which were reported in the *Lancet* [205]. And section 3.5 describes EEG and adverse event related outcomes for the early part of the study.

Table 3.1: Incremental (cumulative) number of centres eligible to enroll and notify cases to UKISS by month of study.

	Number of centres					
Year	1999		2000		2001	
Month						
January			11	(92)	2	(148)
February			11	(103)		
March					1	(149)
April			1	(104)		
May			10	(114)		
June	1	(1)	9	(123)		
July	17	(18)	11	(134)		
August	15	(33)	4	(138)		
September	22	(55)	1	(139)	1	(150)
October	18	(73)	6	(145)		
November	8	(81)				
December			1	(146)		

3.1 Administration and progress of the Study

The United Kingdom Infantile Spasm Study was first approved by the South & West Multicentre Research Ethics Committee on 15 April 1998. However, it was necessary to inform the MREC about several issues and to request a number of protocol amendments before the protocol dated September 1998 was approved on 9 October 1998. The protocol was referred to as *Version 2, MREC approved.* These issues are discussed more fully in the section on safety, licensing, and ethical issues on page 90.

The first participant was enrolled on 30 June 1999. The incremental and cumulative numbers of centres eligible to recruit study participants each month is shown in table 3.1 and the accrual of study participants by month of enrolment is shown in tables 3.2 and 3.3 on pages 101 and 102.

The conduct of the study was impeded by delays in recruiting centres, and by a lower rate of notification of cases than had been predicted. The delays in recruitment of centres were attributed to three sources: (1) competing demands

Table 3.2: Accrual of participants 1999–2000 inclusive.

	Randomised	Non-randomised	Notified only	Total
1999				
June	1	0	0	1
July	0	0	0	0
August	0	0	0	0
September	0	0	0	0
October	3	2	3	8
November	2	0	3	5
December	1	1	0	2
Cumulative	7	3	6	16
2000				
January	4	2	0	6
February	3	1	1	5
March	3	2	1	6
April	2	0	1	3
May	3	2	6	11
June	6	1	1	8
July	4	4	0	8
August	4	2	4	10
September	1	2	3	6
October	3	1	3	7
November	2	0	0	2
December	2	3	1	5
Cumulative	44	23	27	94

Table 3.3: Accrual of participants 2001–2002 inclusive.

	Randomised	Non-randomised	Notified only	Total
2001				
January	3	2	3	8
February	0	6	2	8
March	5	3	1	9
April	2	2	1	5
May	4	4	2	10
June	5	4	3	12
July	1	5	0	6
August	4	4	0	8
September	4	1	0	5
October	4	4	0	8
November	5	4	0	9
December	1	1	1	3
Cumulative	82	63	40	185
2002				
January	1	2	1	4
February	2	3	1	6
March	4	1	0	5
April	2	2	1	5
May	3	3	0	6
June	4	3	0	7
July	3	4	1	8
August	3	3	1	7
September	1	5	2	8
October	1	7	0	8
November	0	4	1	5
December	1	0	1	2
Cumulative	107	100	57[1]	264

[1] Eight *notified only* cases had no recorded notification date.

upon local investigators; (2) delays in approval being granted by local research ethics committees; and (3) delays in approval being granted by the responsible members of NHS trust management. We investigated these sources of delay and attempted to reduce the delays by amending the administration of the study.

3.2 Sample size requirements and estimates of accrual rate

The estimated accrual rate of between 130 and 340 new cases per year was probably high for several reasons. The estimated incidence rate of infantile spasms and the associated sample size calculation are outlined in sections 20 and 27 of the study protocol. The estimate of the UK birth rate of 800 000 per year is high. The number of live births in the UK in 1997 was 726 000; and that in England & Wales was 642 000. The trend in number of live births has been downward since 1990 and the annual average UK births for the 5-year period 1996–2000 was 630 959 [206]. Second, the estimated enrolment rate assumed that nearly all districts in the UK would be recruited to the study. Third, it assumed that nearly all cases that were eligible would be invited to participate. And fourth, it assumed that nearly all carers who were invited to participate would agree, whereas the proportion of cases accepting participation in a trial is usually less than half [190].

The steering committee thought that a difference in treatment effects as great as 20% would be clinically important. The main outcome measure is a binary response of spasms continuing or having stopped for 48 hours before 14 days of completed treatment. The steering committee thought that 70% and 50% were likely values for the proportions responding to better and poorer treatments.

The protocol used these estimates for clinically important differences in treatment effect; a two-sided α value of 0.05 for the type I error associated with the hypothesis test; and a sample size of 250 participants randomly allocated treatments in the ratio 2:1:1. The power $(1 - \beta)$ to detect a difference as great or greater than that considered clinically important between groups given either hormonal treatments or vigabatrin was 88%. The power to detect the same difference between the groups given either prednisolone or tetracosactide was 55%.

This sample size calculation was performed before some important information became available. First, the publication of the randomised trial performed by Vigevano and Cilio [187]. And second, the finding of a lower than expected notification rate for UKISS. The section on problems with accrual provides details of sample size calculations that used scenarios suggested by this new information.

The sample size requirements were recalculated using different assumptions about differences in effect in order to estimate the power associated with smaller sample sizes. These results are shown in table 3.4. The comparison that assumes a 70% response to the better treatment and 50% response to the poorer treatment was that used in the original UKISS power calculation. The 76% *vs* 48% comparison and sample size of 42 represents the study of Vigevano & Cilio, which had a 33% power to detect the reported difference [187]. The difference they found was 8% greater than that assumed for the original UKISS calculation. The 75% *vs* 50% comparisons with different sample sizes assume a difference in treatment effect closer to that of the study of Vigevano and Cilio.

These power calculations suggest that, if the difference in treatment effect is greater by a 5% difference than that of the original UKISS power calculation, the power would be nearly as great with a sample size of 150 participants rather than 250 participants.

Table 3.4: Power calculations given different assumptions about proportions responding in each main treatment group.

Differences in effect	Total number	Power (%)
70% *vs* 50%[1]	250	88
	200	79
	150	65
	120	54
	110	49
	100	45
	80	36
76% *vs* 48%[2]	42	33
75% *vs* 50%[3]	150	86
	100	66
	80	55

[1] Difference used for the original UKISS sample size calculation.
[2] Difference detected by Vigevano and Cilio [187].
[3] Difference assumed in order to reassess UKISS sample size requirements.

3.2.1 Study of local research ethics committee response times

As well as qualitative problems with LREC roles, there were appreciable delays in approving the study. Studies with approval from multicentre research ethics committees (MRECs) are, according to guidelines issued by the Department of Health in 1998, supposed to be approved by LRECs within 21 days of submission [207]. The reason for submission is to ensure that there are no specific ethical issues that pertain to that locality and there is the possibility, of course, that there might be some compelling reason not to grant approval locally. We studied prospectively the time taken for such approval to be granted and published a short paper describing our findings [204]. These data are shown in tables 3.5 and 3.6 on pages 106 and 107.

Table 3.5: Response times of 99 local research ethic committees for submission made between September 1998 and September 1999.

	Median (5th–95th centile) response time in days	**Number (%) of committees responding within 21 days**
Time of submission[1]		
Earlier (n = 48)	26 (6–57)	15 (31)
Later (n = 51)	28 (3–98)	18 (35)
Type of committee[2]		
Fast track (n = 44)	30 (4–85)	14 (32)
Standard (n = 55)	25 (7–64)	19 (35)
Total (n = 99)	28 (4–73)	33 (33)

[1]Earlier submissions were those received before April 1999.

[2]Fast-track committees stated an intention to use executive subcommittees.

Table 3.6: Numbers of documents required and first decisions of 99 local research ethic committees.

	Median (5th–95th centile) number of document copies required	**Number (%) of submissions approved after first review**
Time of submission		
Earlier (n = 48)	4 (1–15)	39 (81)
Later (n = 51)	4 (1–15)	43 (84)
Type of committee		
Fast track (n = 44)	3 (2–13)	35 (80)
Standard (n = 55)	11 (1–15)	47 (85)
Total (n = 99)	4 (1,15)	82 (83)

Earlier submissions were those received before April 1999. LRECs classified as fast-track were those that had stated an intention to use executive subcommittees in order to speed the processing of MREC-approved studies. Only one third of LRECs approved the study within the 21 days recommended by the NHS Executive. Committees that used an executive subcommittee in order to expedite approval of MREC-approved studies did not make quicker decisions. However, such committees did require significantly fewer copies of MREC correspondence and protocols.

3.2.2 Protocol amendments

In response to comments from LRECs, two protocol amendments were developed, approved by the UKISS steering committee, approved by the MREC, and distributed to LRECs and local investigators. These were approved by the MREC on 11 May 2000 and 30 April 2001.

An extra information sheet for parents or guardians was submitted to the MREC for approval on 11 May 2000, and was approved on 12 June 2000. It addressed most of the criticisms that had been made by LRECs during the first 11 months of the study by providing an explanation for carers. This extra information became a protocol amendment and is included in appendix B.2. This amendment provided information relating to the potential risks of visual field loss with vigabatrin; it clarified that the dose of prednisolone being used in the study is higher than typically used in clinical practice for most conditions; it made an explanation the prednisolone is structurally slightly different from corticosteroids that are produced in vivo; and it provided information about the appropriate timing of immunisations after the administration of prednisolone or tetracosactide.

A further protocol amendment was formally approved on 30 April 2001 and the relevant changes are shown in appendix B.3. In addition to the pre-

vious information, this amendment provided extra safety information relating to the risks of intercurrent infection while being treated with prednisolone or tetracosactide.

3.2.3 Effects of need for NHS trust management approval

Approval of the study by responsible members of the local NHS trust was required for three reasons. First, such approval is required for any study that is not sponsored by a member of the ABPI in order for the NHS indemnity arrangements to apply. These indemnity arrangements are regulated by the NHS Litigation Authority (NHSLA). Second, there is a requirement to register research and development programs that are being performed within the NHS. Most NHS trusts have a research and development department that takes responsibility for this. And third, the NHS trust needs to consider any effects new research projects might have upon the use of human and material resources. This third consideration includes external or internal funding, and is often monitored by the research and development department of the trust.

While recruiting in the earlier part of the study, the lead local investigator was asked for the name of the person thought to be responsible for handling the NHS trust approval of new research projects. It soon became clear, however, that the most appropriate person to whom to make a submission for NHS trust management approval was the chief executive of the trust. Tasks tended to be delegated more quickly by chief executives than by other managers, though we did not formally record response times to requests for management approval. Trusts managed the approval of UKISS in a variety of ways, and the study did not have a protocol for obtaining such approval. A letter from an appropriate member of the trust management, such as the chief executive or the medical director, was regarded as being sufficient evidence of approval.

3.2.4 Problems with accrual of participants

Enrolment of participants was slower than expected for several reasons. First, the estimates of accrual rate were over-optimistic since it made no allowance for the proportion of families approached who were likely to decline the offer to participate in the study. A personal communication from the UKISS trial steering committee statistician, Dr Anthony L. Johnson, indicated that the proportion of potential participants finally enrolling in studies with which he had been involved was around 50%. Second, there were delays due to changes in licences for study drugs. Third, there were delays in LREC and in NHS trust management approval of the study in each district, as discussed above. And fourth, some districts appeared not to notify cases that were eligible for inclusion in the study.

Cumulative recruitment of districts is shown in table 3.1 on page 100. When the first case was enrolled, on 31 June 1999, there were 18 districts approved to notify cases. Six months later, 81 centres were approved. By the end of June 2000, this number had risen to 119.

By the end of one year from the enrolment of the first participant, 52 participants had been notified. Of these, 27 were enrolled in the randomised trial, 10 were enrolled in the epidemiology study, and 14 were merely notified. The monthly accrual and cumulative accrual of cases is shown in tables 3.2 and 3.3 on pages 101 and 102. Of the 52 notified cases, 22 were reported from a district notifying one case only, 12 were from districts that had notified 2 cases, 6 were from districts that had notified 3 cases, and 12 were from centres that had reported 6 cases. Thus, 58% of cases were from districts notifying more than one case. However, of the 32 districts that had notified any cases, 69% had reported only one case.

Survey of number of potential participants

A brief survey was made of lead local investigators in the last week of June 2000. The questionnaire asked about potential study participants not notified, and whether they had declined invitation or not been invited to participate. It was sent to lead local investigators in districts that were approved to enrol participants at that time.

An informal analysis of notified cases suggested that potential participants were not being notified from some districts, and that there were important variations in reporting from region to region. In particular, at the end of the first year, there were fewer than expected reports from North and South Thames regions, and from the Trent region. We thought that the most likely explanation for the poor notification rate was likely to be that investigators had not been reminded sufficiently frequently. Because of this, we increased the frequency of newsletters, and circulated them to all local investigators. Also, we sent newsletters designed for EEG departments. Other interventions aimed at increasing and maintaining awareness of the study were: a poster advertisement in the mail sent to 6,200 members of the of the Royal College of Paediatrics and Child Health with its quarterly newsletter, and a short article in the *BACCH Newsletter*, the newsletter of the British Association of Community Child Health. As can be seen from tables 3.2 and 3.3, the response to these interventions was not associated with a marked increase in enrolment and notification. However, it is likely that the interventions helped to sustain awareness and interest in the study.

Review of sample size requirements

At this stage of the study, where it was evident that the rate of accrual was substantially lower than had been predicted, a review of sample size require-

ments. There were two main motivations for this review. First, the randomised trial reported by Vigevano and Cilio showed a larger difference in treatment effects than was assumed during the calculation of sample sizes for UKISS. Second, the notification of cases to the UKISS trial centre was lower than had been expected, and we wished to review the time it was likely to take to recruit a number of participants sufficient to provide useful information. The details of these revised power calculations are given in section 3.2 and table 3.4.

These sample size calculations showed that the study by Vigevano and Cilio had a low statistical power (33%) to detect a difference as great as the one it actually found, and that UKISS would need 140 participants in order to detect the same difference as that found by Vigevano and Cilio with a power of 90%. This information was considered valuable and was thought likely to influence decisions on stopping the study before the planned accrual of 250 randomised participants.

The trial steering committee estimated that funding for the study would not extend beyond December 2002. It considered that aiming for accrual of 120 participants, with an 80% power to detect the 20% difference in effect for the primary comparison of hormonal treatments against vigabatrin, was a reasonable approach.

3.3 Patient characteristics

By December 2002, the study had enrolled participants over a 31-month period from June 1999. Of 208 infants whose eligibility for enrolment in the randomised trial was assessed, 107 were allocated randomised treatment (figure 3.1). Of the 107 participants in the RCT, 64 (60%) were male. The baseline characteristics of study participants are shown in table 3.7 on page 115. Data for the variables *age at onset of spasms* and *duration of spasms at time of randomisa-*

tion were collected from local investigators to the nearest whole month. The median duration of spasms was unknown for 6 infants (2 infants allocated prednisolone, 1 infant allocated tetracosactide, and 3 infants allocated vigabatrin).

The risk factors for neurodevelopmental delay were used as criteria for stratified randomisation. Some infants had more than one of these risk factors (table 3.8 on page 116). There were no striking imbalances in baseline characteristics between the three treatment groups. An analysis of the value of the variables used for stratified randomisation is shown in section 3.4.4.

3.3.1 Ineligible patients

Information about ineligible patients is available for infants who were excluded from the randomised controlled trial and included in the non-randomised study. However, information is not available for infants who were solely notified to the UKISS trial centre. Approximately two-thirds of infants excluded from the randomised trial were ineligible because the parents or guardians preferred a non-randomised treatment to be administered (figure 3.1). Approximately one-third (29 infants) were excluded because they met one or more of the randomised trial exclusion criteria. Tuberous sclerosis, either diagnosed definitively or highly suspected (probably because of a family history of tuberous sclerosis) was the reason for exclusion in approximately half (14/29) of these cases. In one case it was considered that the parents were not able to assess the presence or frequency of spasms reliably, and in another case the local investigator had a strong preference for one of the trial drugs, even though the parents were apparently agreeable to the idea of giving a treatment allocated randomly. In 6 cases, randomisation was precluded by delays and administrative problems related to verifying ethical and management approval of the study.

Figure 3.1: Flow diagram showing disposition of participants assessed for inclusion and enrolled in the UKISS randomised trial, and analysis at study day 14.

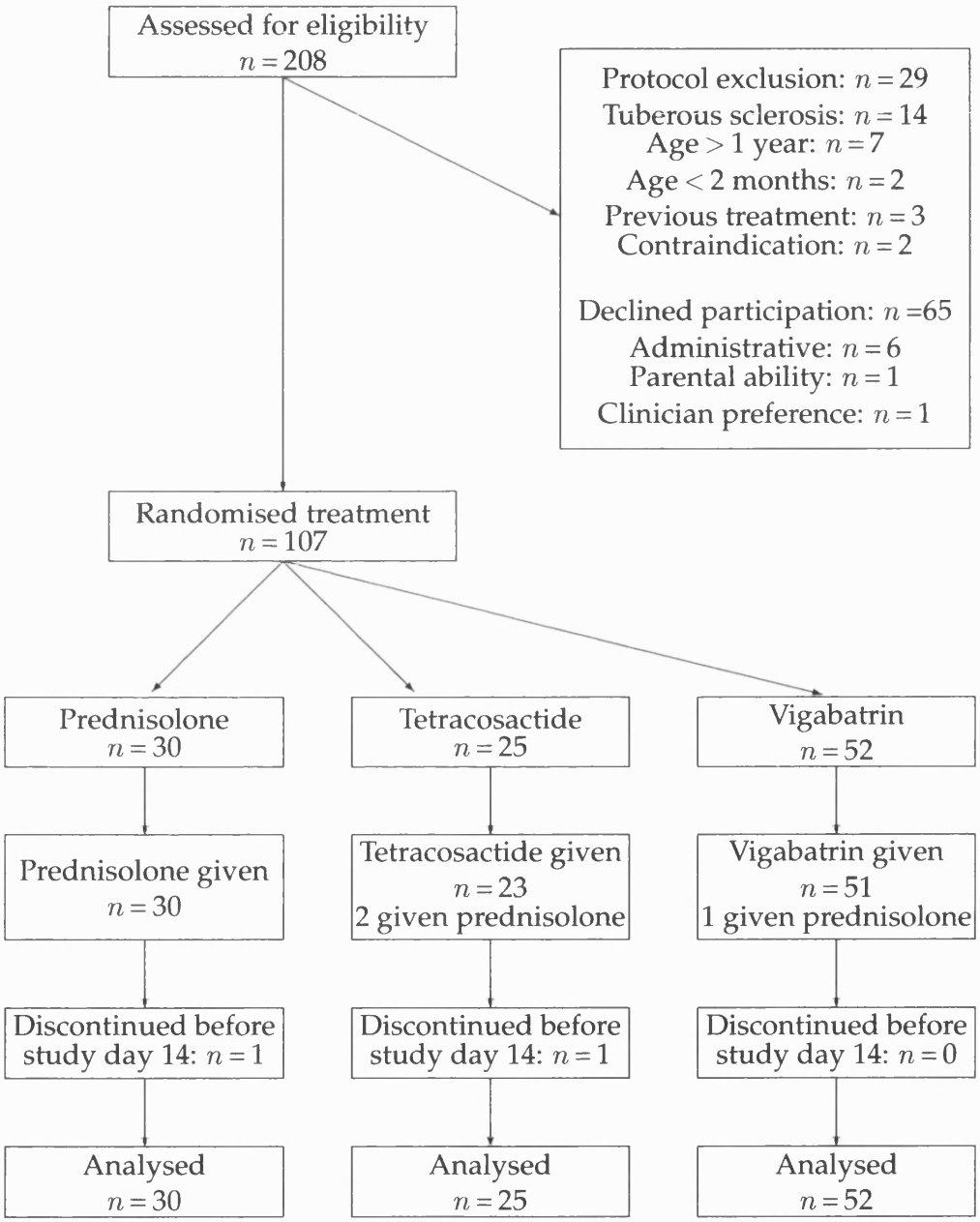

Table 3.7: Baseline characteristics of UKISS randomised trial participants (1).

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Number allocated randomised treatment	30	25	55	52
Male	18	14	32	32
Female	12	11	23	20
Median (range) age in months at onset of spasms	5 (0–10)	5 (0–10)	5 (0–10)	5 (0–10)
Age at randomisation				
60 to 119 days	1	2	3	3
120 to 179 days	11	8	19	17
180 to 239 days	7	8	15	13
240 days and older	11	7	18	19
Median age (range) in months at randomisation	6 (3–10)	6 (3–11)	6 (3–11)	6 (2–11)
Median duration (range) in months of spasms at randomisation[1]	0 (0–8)	1 (0–4)	1 (0–8)	1 (0–6)

[1] Median duration of spasms was unknown in 6 cases.

Table 3.8: Baseline characteristics of UKISS randomised trial participants (2).

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Higher risk of neurodevelopmental delay[1]	15	12	27	22
Chromosomal abnormality	2	0	2	2
Syndrome	3	2	5	2
Neonatal encephalopathy with seizures	4	5	9	8
Cerebral palsy before onset of spasms	8	4	12	10
Delayed development before spasms	13	12	25	19
Underlying aetiology				
Prenatal	8	6	14	15
Perinatal	5	3	8	9
Postnatal	2	1	3	0
Uncertain classification	2	2	4	6
No cause found	13	12	25	21
Not known[2]	0	1	1	1

[1] Some of these infants had more than one risk factor for neurodevelopmental delay.

[2] Cranial neuroimaging not available.

3.3.2 Baseline classification of underlying aetiology

The study protocol did not specify details of aetiological categories to be used in analysis of data, but it stated that such analysis would include diagnostic subgroups such as cerebral dysgenesis, chromosomal anomalies, and metabolic diseases (section 23 of ukiss study protocol). The pre-randomisation stratification variable used to dichotomise infants with higher from lower risk of poor developmental outcomes was a composite of known or highly suspected underlying aetiology and known developmental delay. In order to standardise this process, we later decided to use the *Paediatric Adaptation of ICD-10 (The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, 1992)*, which was published by the *Royal College of Paediatrics and Child Health* in 1996. At the time of randomisation, study participants were classified by time of onset of the underlying condition into one of three groups: prenatal, perinatal, or postnatal. Study participants were placed in specific aetiological groups using all information available at the end of the study, rather than at the time of diagnosis alone, thus effectively giving a final diagnosis. The results of these early and final aetiological classifications are shown in tables 3.8 and 3.13 respectively.

3.3.3 Final classification of underlying aetiology

The final classification of cases by underlying aetiology is shown in table 3.9. Underlying aetiology was classified using the paediatric adaptation of the ICD-10. We required cranial imaging, CT or MRI, and scrutiny of history and clinical examination before determining that no underlying cause could be identified. Most infants had additional investigations, in particular ophthalmic examination and urinary metabolic screen.

Table 3.9: Final classification of underlying aetiology in cases allocated random treatments.

Aetiology	Number
Cerebrovascular: infarct or stroke	14
Chromosomal ($n = 4$)	
Down syndrome	2
Deletion chromosome 1q36 and terminal short arm	1
Deletion chromosome 1p36	1
Malformations ($n = 9$)	
Arachnoid cysts	2
Lissencephaly	2
Holoprosencephaly	1
Hydrocephalus	1
Septo-optic dysplasia	1
Dandy-Walker malformation	1
Focal cortical dysplasia	1
Signs & symptoms, not otherwise specified ($n = 6$)	
Dysmorphic features	1
Abnormal basal ganglia	1
Cerebral atrophy	1
Intracerebral calcification	1
Optic nerve hypoplasia	1
Focal arachnoid cyst	1
Hypoxic-ischaemic encephalopathy ($n = 10$)	
Perinatal	9
Prenatal	1
Periventricular haemorrhage/leukomalacia (perinatal)	5
Metabolic or endocrine ($n = 3$)	
Transient neonatal hypoglycaemia	1
Pyridoxine dependency	1
Enzyme deficiency	1
Nervous system, not otherwise specified ($n = 6$)	
Meningitis	3
Cerebral palsy	2
Porencephaly	1
Other: perinatal – maternal drug abuse	2
Total	59

3.3.4 Features of cases from the non-randomised study

It was initially intended that there would be substantial and complete information relating to the incidence of infantile spasms and the proportions of cases with specific underlying causes; and that this information would allow an assessment of the validity and generalisability of information obtained from the randomised controlled trial. This element of the study was smaller and less useful than was originally intended.

Overall, 265 infants were notified to the UKISS trial centre during the course of the study. Of these, no further information was available on 58 cases, and 107 cases were enrolled in the randomised controlled trial and are reported in detail elsewhere in this thesis. One hundred cases were enrolled in the non-randomised study.

These non-randomised cases consisted of 59 male and 41 female infants. Underlying cause was not known in 11 cases because information about investigations and results was incomplete. In 22 cases, there had been extensive investigation and no cause was found. Specific causes were reported in 67 cases, as shown in table 3.10 on page 121.

The treatments allocated to the non-randomised cases were: vigabatrin ($n = 61$), prednisolone ($n = 28$), tetracosactide ($n = 10$), and sodium valproate ($n = 1$). Of the 15 cases classified as having tuberous sclerosis, 11 were treated with vigabatrin, 3 with prednisolone, and 1 with sodium valproate. Information relating to the *cessation of spasms* outcome variable was available for 88 (88%) of the 100 non-randomised cases. Of these cases, the proportion with *cessation of spasms* was 45/88 (51%) and the proportion with *non-cessation of spasms* was 43/88 (49%). *Cessation of spasms* was reported in 20/34 (59%) of those given hormonal treatments and in 25/53 (47%) of those given vigabatrin. This difference is not statistically significant ($\chi^2_{(1)} = 1.13$; $P = 0.29$).

There were 87 cases in which underlying aetiology was reliably classified and the *cessation of spasms* outcome was reported. One case with missing information relating to investigations was classified as a non-responder. In the other 12 cases, aetiological and outcome information were both unavailable. Of those with an identified underlying aetiology, 33/65 (51%) had *cessation of spasms*; and of those without an identified underlying aetiology after extensive investigation, *cessation of spasms* was reported in 12/22 (55%). There was no significant difference in proportions responding by presence or absence of an identified underlying aetiology ($\chi^2_{(1)} = 0.09$; $P = 0.76$).

Cases with tuberous sclerosis are of particular interest since they were excluded from the randomised trial element of the study. Of the 15 cases with tuberous sclerosis, the *cessation of spasms* outcome was known in 14 cases. Of these 14 cases, 10 (71%) had *cessation of spasms* and 4 (29%) were non-responders. *Cessation of spasms* was reported in 8/10 cases given vigabatrin (with outcome being unknown in another single case) and in 2/3 cases given prednisolone. The case treated with sodium valproate was a non-responder.

One of the initial aims of UKISS was to obtain reliable epidemiological data on a large population-based sample of cases from the United Kingdom. However, accrual of cases was slower than planned, and notification and reporting of non-randomised cases was substantially lower than the estimate of incident cases in the UK during the study period. Also, neurodevelopmental assessments were not made on cases who were not randomly allocated treatments. These issues are discussed further in sections 2.3.2, 6.2.10, and 6.2.12. Only very limited inferences can be made from these data, and no further data about non-randomised cases are reported in this thesis. Further information in this chapter and chapter 4 relate to information from the randomised trial component of the study.

Table 3.10: Final classification of underlying aetiology in non-randomised cases.

Aetiology	**Number**
Cerebrovascular: infarct or stroke	2
Chromosomal ($n = 31$)	
Tuberous sclerosis	15
Down syndrome	9
Deletion chromosome 17p13.3	1
Deletion chromosome 22q	1
XYY karyotype	1
Incontinentia pigmenti	1
Muscle-eye-brain disease	1
Neurofibromatosis type 1	1
PEHO syndrome	1
Malformations ($n = 6$)	
Focal cortical dysplasia	2
Lissencephaly	2
Schizencephaly	1
Agenesis of the corpus callosum	1
Signs & symptoms, not otherwise specified ($n = 6$)	
Microcephaly	2
Cerebral atrophy	1
Hemimegalencephaly	1
Hyperintense basal ganglia on MRI	1
Parenchymal heterotopias	1
Hypoxic-ischaemic encephalopathy ($n = 10$)	
Perinatal	7
Prenatal	3
Periventricular haemorrhage/leukomalacia (perinatal)	6
Metabolic or endocrine ($n = 1$)	
Transient neonatal hypoglycaemia	1
Nervous system, not otherwise specified ($n = 5$)	
Encephalitis	2
Meningitis	2
Cerebral palsy	1
Total	67

3.3.5 Compliance with treatment protocol

Although tolerance limits for compliance were not stated in the study protocol, we later decided that we would consider any child to have complied fully with the treatment protocol if drug doses were within 10% of those stated in the study protocol, if the frequency of administration was appropriate, and if any changes to the regimen were made within 24 hours of that stated in the study protocol [205]. Although the study protocol was not explicit that the day of randomisation was considered to be *study day 0* and some local investigators might have made changes based on the assumption that this was *study day 1*, we felt that a 24-hour tolerance limit was appropriate and not over-conservative.

The dose was reported as given in full compliance with the protocol in 21/30 (70%) infants allocated prednisolone, 16/25 (64%) of those allocated tetracosactide, and 29/52 (56%) of those allocated vigabatrin. In 18 infants (5/30 (17%) of those allocated prednisolone, 4/25 (16%) allocated tetracosactide, and 9/52 (17%) allocated vigabatrin) the regimen given was appropriate given that adverse events were reported and justified amendment of the treatment regimen. In 11 infants (1 allocated prednisolone, 5 allocated tetracosactide, and 5 allocated vigabatrin) we were unable to verify that the regimen accorded fully with the study protocol, and in 12 infants (3 allocated prednisolone, and 9 allocated vigabatrin) we were certain that there had been deviation from the study protocol.

An alternative or additional treatment for spasms was administered after allocation of randomised treatment and before study day 14 in the case of 6 infants: 2 infants allocated prednisolone received vigabatrin; 3 infants allocated vigabatrin received prednisolone; and 1 infant allocated vigabatrin received lorazepam. Prior treatment for seizures other than infantile spasms was con-

tinued during study days 0 to 14 in 32 infants (9 allocated prednisolone, 9 allocated tetracosactide, and 14 allocated vigabatrin). Four infants received pyridoxine (1 allocated prednisolone and 3 allocated vigabatrin). In one infant there appeared to be response to pyridoxine, relapse of seizures after later withdrawal of the pyridoxine, and secondary response after pyridoxine was reintroduced. This case met criteria for the diagnosis of pyridoxine dependent seizures.

3.3.6 Completion of study diaries

Diaries containing information about spasms and treatment during study days 0 to 14 were returned to the study centre in 91/107 (85%) of cases (24/30 (80%) allocated prednisolone, 21/25 (84%) allocated tetracosactide, and 46/52 (88%) allocated vigabatrin).

3.4 Primary clinical response: *cessation of spasms*

3.4.1 Proportions with *cessation of spasms*

The primary outcome of *cessation of spasms*, defined as absence of observed or reported spasms for at least 48 consecutive hours and for a period that included study days 13 and 14, was reported in a significantly higher proportion of infants allocated hormonal treatments than infants allocated vigabatrin: 40/55 (73%) *vs* 28/52 (54%) (difference 19% (95% CI 1% to 37%); $\chi^2_{(1)} = 4.11$; $P = 0.04$). The *cessation of spasms* outcome, stratified by underlying aetiological category, is shown in table 3.11. There were no significant differences in the proportions with *cessation of spasms* between the two hormonal treatment groups: 19/25 (76%) in those allocated tetracosactide and 21/30 (70%) in those allocated prednisolone. Two infants allocated tetracosactide were in

Table 3.11: Numbers with *cessation of spasms* by treatment and by underlying aetiological category.

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Prenatal	6/8	5/6	11/14	7/15
Perinatal	3/5	3/3	6/8	5/9
Postnatal	1/2	1/1	2/3	0
Other	2/2	0/2	2/4	3/6
Undetermined	9/13	10/13	19/26	13/22
All categories	21/30	19/25	40/55	28/52

fact given prednisolone as the first-line treatment, and both of these infants were reported to have *cessation of spasms*. The reason for these infants being given prednisolone rather than tetracosactide was that the parents expressed a wish to avoid intramuscular injection. They were permitted into the study because it was considered at the time of randomisation that their inclusion (with an agreement to administer prednisolone in place of tetracosactide if necessary) would not alter the primary comparison of hormonal treatments against vigabatrin. In addition, one infant allocated vigabatrin was in fact given prednisolone as first-line treatment, again because of parental preference stated after allocation of randomised treatment, and this infant was also reported to have *cessation of spasms*. If an analysis were to be made by initial treatment administered rather than by intention to treat, there would be a marginally larger difference in responses between hormonal treatments and vigabatrin (41/56 (73%) *vs* 27/51 (53%)) and a marginally smaller difference between tetracosactide and prednisolone (17/23 (74%) *vs* 23/32 (72%)).

3.4.2 Time to *cessation of spasms*

Since time to cessation of spasms is conditional upon a response at study day 14, the variable *time to cessation of spasms* was reported as the number of consecutive days known to be spasm-free at the end of study day 14. In the case of 7 infants who did not have *cessation of spasms* (4 allocated hormonal treatments and 3 allocated vigabatrin) the reported information did not indicate whether spasms were present on both days 13 and 14 or on only one of these days. Their number of consecutive days free of spasms was not known and was set to zero. One infant allocated a hormonal treatment was known to be free of spasms on days 13 and 14 but the day of response was uncertain. This infant's number of consecutive days free of spasms was set at two days. The median (25th, 75th) number of consecutive days spasm-free at the end of study day 14 was 9 (1, 12) for those allocated hormonal treatments and 2.5 (0, 12) for those allocated vigabatrin (Wilcoxon rank-sum test $P = 0.04$). This analysis was performed by Dr Anthony L. Johnson, the study statistician.

3.4.3 Factors potentially biasing *cessation of spasms* outcome

Cessation of spasms and age at onset of spasms

There was no obvious trend in proportions responding according to age at onset of spasms (table 3.12).

Cessation of spasms and *lead-time to treatment*

Since delays in treatment might be associated with poorer outcomes, we investigated the effect of *lead-time to treatment*; that is, duration of spasms before treatment intervention. Precise dates identified by history as being the date of onset of clinical spasms were reported in 44/107 (41%) of enrolled infants. The range of reported durations between onset of clinical spasms and date of ran-

domisation in these 44 infants was 2 to 102 days. For 96/107 (90%) of infants, the duration of spasms could be reliably classified into one of two groups: less than or equal to one month (one month taken as being 30 days) and one month or longer. The duration of spasms could not be reliably classified in 11 cases. Of those that were categorised, 61/96 (64%) had spasms for one month or less, and 35/96 (35%) for longer than one month.

Lead-time to treatment did not significantly predict *cessation of spasms*, which was reported in 41/61 (67%) of infants with a lead-time of less than 1 month and in 21/35 (60%) of those with lead-time of greater than 1 month (difference 7% (95% CI −13% to +27%); $\chi^2_{(1)} = 0.51$; $P = 0.48$).

Cessation of spasms and underlying aetiology

Cases classified by underlying aetiological categories are shown in table 3.13. As can be seen from this table , there were relatively sparse data for any one specific underlying aetiology, but the outcome variable *cessation of spasms* did not vary substantially between underlying aetiological groups. The proportions of infants with *cessation of spasms* were similar in the groups of infants dichotomised as having or not having an identified underlying aetiology: (36/59 (61%) *vs* 31/46 (67%), difference −6% (95% CI −25% to +12%); $\chi^2_{(1)} = 0.45$; $P = 0.50$). Two infants were not classified into aetiology known or not known groups because they had not had neuroimaging studies and classification could not be made reliably.

Table 3.12: *Cessation of spasms* by age at onset of spasms.

	Age in months										
	1	2	3	4	5	6	7	8	9	10	**Total**
Cessation of spasms	1/1	4/7	6/9	11/21	12/19	14/15	10/12	4/7	3/4	2/6	67/101
Percentage	100%	57%	67%	52%	63%	93%	83%	57%	75%	33%	66%

Age at onset not reliably determined in 6 cases.

Cessation of spasms and baseline EEG features

Cessation of spasms did not differ significantly between groups with or without reported hypsarrhythmia in the baseline EEG. Of 83 infants with baseline EEGs reported as hypsarrhythmic, 53 (64%) had *cessation of spasms*, compared with 15/24 (63%) of those whose baseline EEG was not reported as hypsarrhythmic. The respective proportions by treatment group were 30/39 (77%) and 10/16 (63%) for infants allocated hormonal treatments, and 23/44 (52%) and 5/8 (63%) for infants allocated vigabatrin. More detailed analysis of baseline EEG characteristics by modifying features is not practicable because the form and content of reporting was not standardised.

3.4.4 *Cessation of spasms* and stratified randomisation variables

Stratified randomisation was used to reduce the risk of any significant imbalance in important prognostic factors between treatment groups. The variables used for this stratified randomisation were sex, age category at randomisation, and aetiological categorisation at randomisation. These are described in more detail in section 5 of the UKISS study protocol (page 246). Their value was assessed by examining any associations they might have with the variable *cessation of spasms*.

The relationship between cessation of spasms and sex is shown in table 3.14. Cessation of spasms occurred in 43/64 (67%) of males and 25/43 (58%) of females, a difference that is not statistically significant (9% (95% CI −10% to +28%); $\chi^2_{(1)} = 0.91$; $P = 0.34$). Stratified randomisation age category also had no significant association with *cessation of spasms* (Pearson $\chi^2_{(3)} = 4.60$; $P = 0.21$) and no evident trend. Three cases were allocated to wrong age categories at randomisation. An infant with *cessation of spasms* aged 179 days at enrolment

Table 3.13: *Cessation of spasms* by final aetiological category.

Aetiology	*n*	*Cessation of spasms* Number	(%)
Cerebrovascular	14	10	(71%)
Chromosomal	4	2	(50%)
Malformation	9	4	(44%)
Signs and symptoms NOS	6	3	(50%)
Hypoxic-ischaemic encephalopathy	10	5	(50%)
PVH/PVL	5	5	(100%)
Metabolic or endocrine	3	1	(33%)
Nervous system	6	4	(66%)
Other	2	2	(100%)
Known cause	59	36	(61%)
No cause found	46	31	(67%)
Not known	2	1	(50%)
Total	107	68	(64%)

Table 3.14: *Cessation of spasms* by stratified randomisation sex category.

	Cessation of spasms		
Sex	**Yes**	**No**	**Total**
Male	43	21	64
Female	25	18	43
Total	68	39	107

Table 3.15: *Cessation of spasms* by stratified randomisation age category.

	Cessation of spasms		Total
Age category	**Yes**	**No**	
60–119 days	4	2	6
120–179 days	19	17	36
189–239 days	23	7	30
240 days and older	22	13	35
Total	68	39	107

was allocated treatment from the *180–239 days old* age randomisation stratum; an infant with *cessation of spasms* aged 265 days at enrolment was allocated treatment from the *120–179 days old* age randomisation stratum; and an infant who was a primary clinical non-responder aged 211 days at enrolment was allocated treatment from the *240 days and older* age randomisation stratum. After adjustment for this misclassification, the values for the chi-square test are not substantially different ($\chi^2_{(3)} = 4.06$; $P = 0.26$). Table 3.15 shows these proportions after adjustment for misclassification at the time of randomisation. Table 3.16 shows the numbers with *cessation of spasms* by the stratified randomisation composite aetiological categories. Although cessation of spasms was commoner in infants who had normal development preceding diagnosis of spasms and no identified underlying aetiology at the time of enrolment, the differences between the two aetiological categories was not significant (28/49 (57%) *vs* 40/58 (69%), difference −12% (95% CI −30% to +6%); $\chi^2_{(1)} = 1.60$; $P = 0.21$).

Table 3.16: *Cessation of spasms* by stratified randomisation composite aetiology category.

	Cessation of spasms		Total
Stratified category	Yes	No	
Delayed development or known aetiology	28	21	49
Normal development and no known aetiology	40	18	58
Total	68	39	107

3.5 Other early outcomes

3.5.1 Electroencephalographic changes by study day 19

The patterns of reported EEG findings at baseline and during study days 12 to 19 are shown in tables 3.17 and 3.18. Two infants had follow-up EEGs reported as normal despite being classified as non-responders with respect to the primary clinical outcome, *cessation of spasms*. One of these infants had an EEG on study day 18 and the diary reported that the last witnessed spasm was seen on study day 17. The other infant was reported as having a single, non-clustered spasm on each of five days prior to no further spasms being witnessed, and the follow-up EEG was performed on one of these final 5 days.

Six infants had *cessation of spasms* but EEGs that were reported as showing hypsarrhythmia. Using the outcome that is suggested in chapter 5 as constituting a primary electroclinical outcome – that is, cessation of clinical spasms and resolution of hypsarrhythmia – electroclinical response was confirmed in 38/55 infants allocated hormonal treatments and 24/52 infants allocated vigabatrin. These differences are statistically significant (23% (95% CI 5% to 41%); $\chi^2_{(1)} = 5.77$, $P = 0.02$) but are subject to potential bias since EEG outcomes were not recorded within the set time limits for 10 infants allocated hormonal treatments and 9 infants allocated vigabatrin. Performing a sensitivity analysis that

assumes all unrecorded vigabatrin cases had resolution of hypsarrhythmia and all unrecorded hormonal treatment cases had continuing hypsarrhythmia gives a non-significant result (difference 6% (95% CI −12 to +24%); $\chi^2_{(1)} = 0.38$, $P = 0.54$).

3.5.2 Adverse events at study day 14

No infants died during the period up to study day 14, but treatment was stopped due to reported adverse events in two infants. In the case of one infant allocated prednisolone, treatment was stopped due to reported vomiting and hypertension, though the *Day 14* report gave no indication of significant systemic hypertension and the local investigator was noted to have commented that he would have preferred the treatment randomisation process to have resulted in allocation of vigabatrin and that he had concerns about the risks of adverse events with prednisolone. One infant allocated tetracosactide responded with cessation of spasms but was withdrawn from treatment after developing a rash.

Adverse events were reported in 30/55 (55%) of infants allocated hormonal treatments (19/30 (63%) prednisolone and 11/25 (44%) tetracosactide) and 28/52 (54%) allocated vigabatrin (table 3.19). Four infants had a reduction in treatment doses without complete cessation of treatment, and 12 infants continued treatment but with deferred increases in the treatment regimen. With respect to these outcomes, there were no significant differences between treatment groups.

Table 3.17: Classification of baseline and follow-up EEG. reports

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Baseline EEG hypsarrhythmic	16/30 (53%)	23/25 (92%)	39/55 (71%)	44/52 (85%)
Follow-up EEG Performed	23/30(77%)	20/25 (80%)	43/55 (78%)	46/52 (88%)
Follow-up EEG[1]				
Normal	5/23 (22%)[2]	1/20 (5%)[3]	6/43 (14%)	6/46 (13%)[4]
Abnormal but non-hypsarrhythmic	14/23 (61%)	17/20 (85%)	31/43 (72%)	20/46 (43%)
Hypsarrhythmic	4/23 (17%)[5]	2/20 (10%)[5]	6/43 (14%)	20/46 (43%)[6]

[1] Valid follow-up EEGs were those performed between study days 12 and 19.
[2] Baseline EEG was hypsarrhythmic in 4/5.
[3] Baseline EEG was hypsarrhythmic.
[4] Baseline EEG was hypsarrhythmic in 5/6.
[5] One infant with hypsarrhythmic follow-up EEG had *cessation of spasms*.
[6] Four infants with hypsarrhythmic follow-up EEG had *cessation of spasms*.

Table 3.18: EEGs at baseline and follow-up by allocated treatment and primary clinical response, stratified by presence or absence of hypsarrhythmia in baseline EEG.

	Hormonal Treatment						**Vigabatrin**	
	Prednisolone		**Tetracosactide**		**Combined**			
Baseline hypsarrhythmia	Present	Absent	Present	Absent	Present	Absent	Present	Absent
Follow-up EEG								
Hypsarrhythmia	4	1	2	0	6	1	16	1
Responder	1	0	1	0	2	0	4	0
Not hypsarrhythmia	10	10	16	2	26	12	20	6
Normal EEG	4	1	1	0	5	1	4	1
EEG note done	2	3	5	0	7	3	8	1

Irritability was reported commonly in those allocated hormonal treatments, and significantly more often than with vigabatrin (19/55 (35%) *vs* 2/52 (4%); $\chi^2_{(1)} = 16.0$, $P < 0.001$)(table 3.20). The most commonly reported symptom with vigabatrin was drowsiness, which was significantly less common with hormonal treatments (14/52 (27%) *vs* 6/55 (11%); $\chi^2_{(1)} = 4.51$, $P = 0.034$). Increased appetite was more commonly reported with hormonal treatments, but the numbers were relatively small and the difference was not statistically significant (7/55 (13%) *vs* 1/52 (2%); two-sided Fisher exact test $P = 0.06$).

Systemic blood pressures in those allocated hormonal treatments were recorded, on one or more occasions, to be above 110/80 mmHg in 11/55 (20%) of infants and above 120/90 mmHg in 8/55 (15%) of infants, with the respective proportions being 7/30 (23%) and 4/30 (13% for those allocated prednisolone, and 4/25 (16%) for both systemic blood pressure levels in those allocated tetracosactide. Two infants allocated prednisolone were given diuretics as an intervention to reduce what was considered by the local investigator to be clinically significant systemic hypertension. Glycosuria was recorded in only 1 infant, which had been allocated tetracosactide, but no infants developed diabetes mellitus and none were treated specifically for hyperglycaemia. There were no reported adverse events for the 3 infants who received prednisolone but had been randomly allocated tetracosactide or vigabatrin, although one was reported to have at least one systemic blood pressure measurement over 120/90 mmHg without any specific intervention.

Table 3.19: Number of adverse events reported during study days 1–14 by intention-to-treat.

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Allocated treatment	30	25	55	52
Adverse events	19	11	30	28
Treatment stopped	1	1	2	0
Treatment reduced	1	1	2	2
Increase avoided[1]	3	2	5	7
Treatment not altered	14	8	22	19

[1] That is, treatment not increased as protocol suggested.

Table 3.20: Types of adverse events reported during study days 1–14 by intention-to-treat.

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Gastrointestinal	7	5	12	11
Irritability	12	7	19	2
Drowsiness	5	1	6	14
Infection	3	0	3	5
Increased appetite	4	3	7	1
Dermatological	1	3	4	2
Fluid/electrolyte/BP[1]	3	2	5	0
Neuropsychiatric[2]	1	0	1	4
Hypertonia	0	2	2	0
Varicella exposure[3]	1	1	2	0
Other	3	4	7	5

[1] Includes hypertension and any disturbance of fluids or electrolytes.

[2] Most commonly sleep disturbance.

[3] Varicella exposure requiring zoster immunoglobulin since presumed immunosuppression.

3.6 Summary of UKISS early outcomes

The most striking finding from the early part of UKISS was that the primary clinical outcome, *cessation of spasms*, was reported significantly more frequently in infants allocated hormonal treatments, with a difference in proportions responding that was similar to the clinically important difference of 20% that was used for the original power calculation for this study. The effect estimates for the groups allocated prednisolone and tetracosactide were similar. These findings are discussed further in chapter 6.

Chapter 4

Later Outcomes from the United Kingdom Infantile Spasms Study

This chapter reports and analyses later outcomes from the United Kingdom Infantile Spasms Study. The protocol provided for these outcomes to be assessed when the study participant reached the age of 12 to 14 months. Section 4.1 describes the conduct of the later part of the study. Sections 4.2 and 4.3 describe neurodevelopmental outcomes and potential factors that might act as prognostic factors or biases for these outcomes. Section 4.4 reports secondary outcomes from the later part of the study, particularly relapse of spasms and progression to other seizure types; and section 4.5 describes adverse events, including deaths, occurring during the study period.

4.1 Conduct of the later part of the study

A final clinical assessment was made on 106 of the 107 enrolled children since one case (study death 1 in section 4.5) died before any routine follow-up assessment was made. The follow-up data after the study day 14 was obtained primarily from forms completed at 3-monthly intervals (UKISS trial folder forms

6a, 6b, and 6c) and from form 7. Form 7 was intended to be completed at the time of final clinical assessment, and only infants who were enrolled before the age of 3 months would have required completion of all forms 6. However, in some cases one of the forms 6 was completed closer to the planned final clinical assessment age of 12–14 months than was form 7, and therefore final clinical assessment information was sometimes taken from one of the forms 6. Final clinical assessment data were taken exclusively from form 7 in 96 cases; from forms 6a, 6b, and 6c in 1, 3, and 2 cases respectively; and from a combination of form 7 with form 6a, 6b, or 6c in 2, 2, and 1 cases respectively.

4.1.1 Ages and duration in study at follow-up assessments

The median age at time of first 3-monthly assessment was 10.4 months (IQR 8.3–12.4; range 6.2–16.6). The median duration of enrolment at the time of completion of the first 3-monthly assessment form was 3.2 months (IQR 2.9–3.7; range 1.7–9.5). The mean (SD) age at time of final clinical assessment ($n = 106$) was 418 (43) days or 13.7 (1.4) months. The range of ages was 352 to 622 days (11.6 to 20.4 months) with a median of 416 days (13.7 months) and interquartile range 386 to 441 days (12.7 to 14.5 months). The median duration of enrolment at the time of final clinical assessment was 6.6 months (IQR 5.1–8.7; range 1.7–12.7). The median age at completion of Vineland Adaptive Behavior Scales was 14.7 months (IQR 14.3–15.1; range 13.8–19.6). The median duration of study enrolment at the time of Vineland assessment was 8.3 months (IQR 6.2–10.0; range 3.1–14.4). These ages and durations, stratified by randomised treatment, are shown in table 4.1. There is no evidence of any significant differences in these ages and durations between treatment groups that might bias the analysis of outcomes.

Figure 4.1: Flow diagram showing disposition of participants in randomised trial at final assessment and Vineland ABC assessment stages.

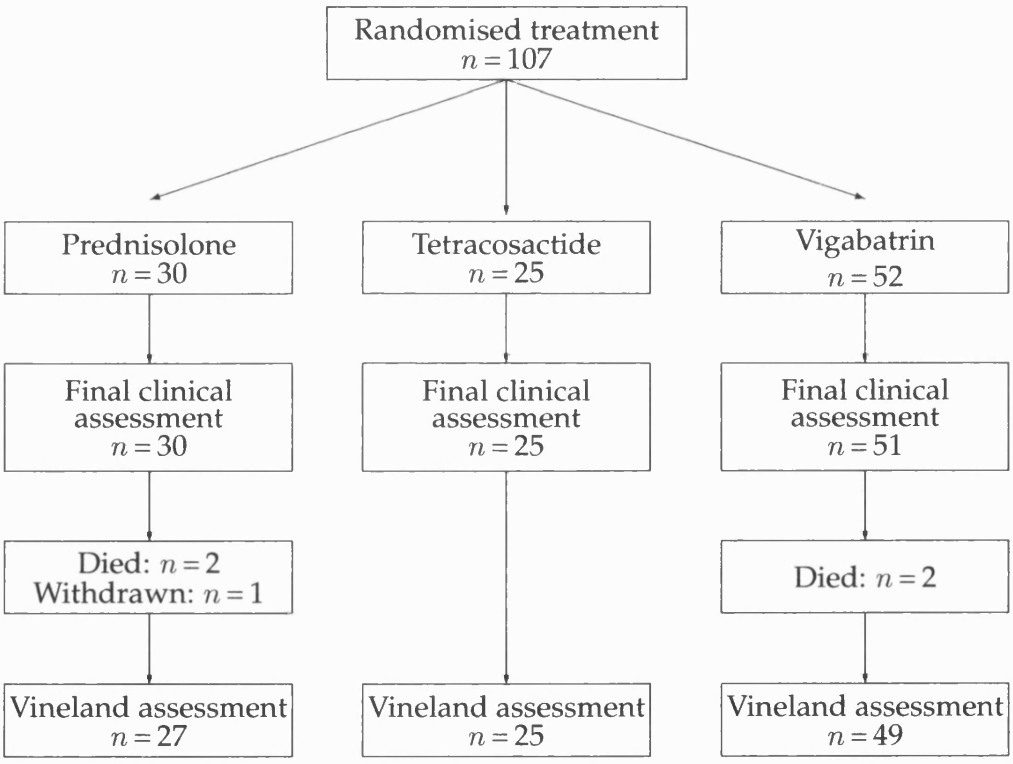

Table 4.1: Ages and duration of study participation (months) at follow-up assessments by randomised treatment.

	Hormonal Treatments			**Vigabatrin**
	Prednisolone	**Tetracosactide**	**Combined**	
First 3-monthly assessment				
Median age (IQR) [1]	9.9 (8.2–12.4)	10.3 (8.8–12.0)	10.1 (8.3–12.4)	10.8 (8.2–16.0)
Median study duration (IQR)	3.1 (2.8–3.5)	3.2 (3.0–4.1)	3.2 (2.9–3.7)	3.1 (2.7–3.7)
Final clinical assessment				
Median age (IQR)	13.9 (12.7–14.6)	13.2 (12.6–14.5)	13.4 (12.6–14.6)	13.7 (12.8–14.5)
Median study duration (IQR)	6.8 (5.5–8.6)	7.8 (5.6–8.7)	7.3 (5.5–8.7)	6.4 (4.5–8.9)
Vineland assessment				
Median age (IQR)	14.7 (14.3–15.0)	14.7 (14.3–15.2)	14.7 (14.3–15.1)	14.8 (14.3–15.1)
Median study duration (IQR)	7.7 (6.0–10.1)	8.7 (6.6–10.0)	8.4 (6.3–10.0)	8.0 (6.0–9.7)

Diary entries for the final week of the study were returned in only 19/106 (18%) of cases. The range of ages for the first day of completion of these diaries during the final week was 365 to 426 days, with a median of 366 days and interquartile range 365 to 370 days.

4.1.2 Conduct of neurodevelopmental assessments

Neurodevelopment was assessed by means of Vineland Adaptive Behavior Scales, as described in section 2.4.10 on page 88. Vineland assessments were made in 101 of the 107 randomised study participants. Five children died before the follow-assessment was made (2 infants allocated prednisolone and 3 infants allocated vigabatrin) and one infant was withdrawn from the study. This last case was withdrawn because of confusion over classification on the part of the local investigator. He informed the trial centre that the child had withdrawn from the study and it was assumed at the trial coordinating centre that the reason for this was withdrawal of parental consent. However, the local investigator later informed the trial centre, when asked to state if there was any stated reason for withdrawal of parental consent, that the intended message was merely that the child was a non-responder with respect to the primary outcome *cessation of spasms*. The local investigator had assumed that primary clinical non-response removed any need for further follow-up. Thus, Vineland assessments were made in 52 children allocated hormonal treatments (27 allocated prednisolone and all 25 allocated tetracosactide) and 49 children allocated vigabatrin.

4.2 Neurodevelopmental outcomes

Descriptive statistics for the Vineland ABC scores by treatment group are shown in table 4.2, and the full distribution of these scores are shown in figure 4.2. The

Table 4.2: Vineland Adaptive Behavior Scales composite scores at age 14 months by treatment group.

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Randomised	30	25	55	52
Died	2	0	2	3
Test not done	1	0	1	0
Score available	27 (90%)	25 (100%)	52 (95%)	49 (94%)
Mean	78.0	78.8	78.4	77.5
SD	15.8	17.8	16.6	12.7
SEM	3.0	3.6	2.3	1.8
Median	74	81	74.5	77
Range	60–114	50–107	50–114	51–107
Interquartile range	65–87	65–97	65–92.5	70–86

overall mean (SD) Vineland ABC score for the 101 children assessed was 78.0 (14.9) with a range of 50 to 114. The overall median Vineland ABC score was 76 and the interquartile range was 67 to 89. Most children enrolled in the UKISS trial had Vineland ABC scores below the population average of 100. Approximately one-third of cases had scores below 2 standard deviations from the mean ($n = 31$ (31%)) and two-thirds had scores at least one standard deviation below the mean ($n = 68$ (67%)). One-third had a Vineland ABC score within one standard deviation of the mean ($n = 33$ (33%)) and 8 of these had scores above the population mean.

Developmental scores for specific aetiological categories are shown in table 4.3. Overall, there were no significant differences in mean (SD) Vineland scores by treatment group (hormonal treatment 78.6 (16.8) *vs* vigabatrin 77.5 (12.7)).

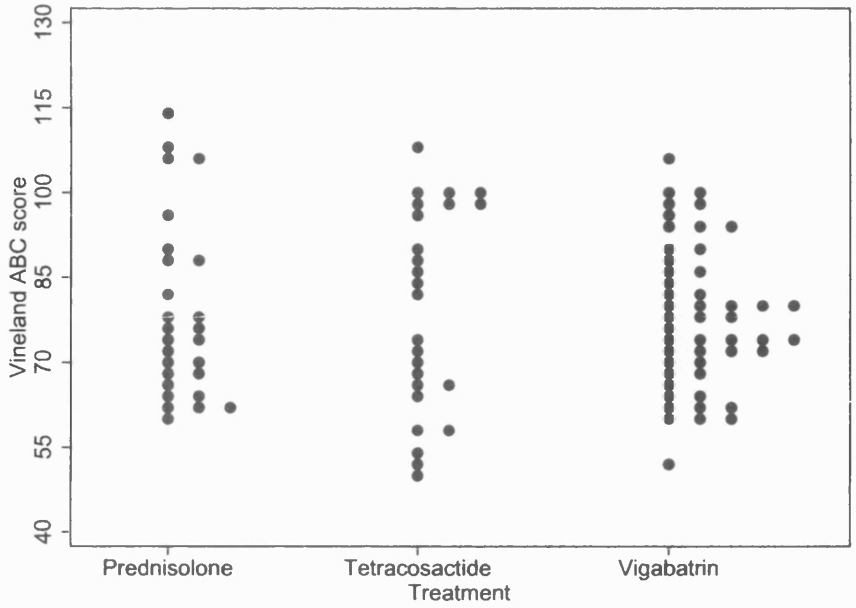

Figure 4.2: Distribution of Vineland ABC scores by treatment group.

There were no significant differences in Vineland ABC score by sex (mean (SD) 79.3 (15.6) for males and 76.4 (13.9) for females).

The subgroup of infants with no identified underlying aetiology was of *a priori* interest. These were investigated by means of an analysis of variance (ANOVA) model with differences for the specific comparison of interest being made by a least significant difference test. The results of this ANOVA model are reported in table 4.4, where the number of observations is 99 and the overall number of degrees of freedom is 95. This ANOVA model shows that the presence of an identified underlying aetiology was associated with significantly lower Vineland ABC scores ($F_{1,95} = 13.80$; $P < 0.001$).

In infants with no identified underlying aetiology, there was a significant difference between treatment groups in mean Vineland ABC score, with scores being higher in those allocated hormonal treatment 88.2 (17.3) compared with those allocated vigabatrin 78.9 (14.3) (least significant difference test $t_{(95)} = 2.28$; P = 0.03; difference 9.3; 95% CI for the difference +1.2 to +17.3). This analysis

Table 4.3: Vineland ABC scores by category of underlying aetiology.

Aetiological category	***n***	**Mean**	**SD**	**Range**
Cerebrovascular	14	79.4	10.0	54–95
Chromosomal	4	74.5	7.5	65–83
Malformations	9	70.4	15.2	51–94
Signs & symptoms NOS	5	71.8	21.3	50-106
HIE	10	69.1	6.6	60–81
PVH/PVL	5	74.2	8.0	65–87
Metabolic/Endocrine	2	76.0	4.2	73-79
Nervous system NOS	4	70.3	6.2	61–74
Other	1	62.0	-	-

Table 4.4: Analysis of variance of Vineland ABC score by randomised treatment and presence or absence of identified underlying aetiology.

Source of variation	**d.f.**	**Mean square**	*F*	*P*
Treatment group	1	109.27	0.59	0.44
Aetiology	1	2548.70	13.80	< 0.001
Treatment × Aetiology	1	1251.59	6.78	0.011
Residual error	95	184.70		

included 45 infants (24 allocated hormonal treatments and 21 allocated vigabatrin). A sensitivity analysis was performed by including the two children who were not reliably classified as having or not having an identified underlying aetiology because they had not had any neuroimaging studies. The sensitivity analysis included these infants in such as way as to reduce the difference found to a minimum. The first of these was a male infant had been allocated vigabatrin and had *cessation of spasms* with a subsequent Vineland ABC score of 93. He was included in the sensitivity analysis as having no identified underlying aetiology. The other case was a female infant that had been allocated tetracosactide, had not had *cessation of spasms*, and had a Vineland ABC score of 57. She was also included in the sensitivity analysis with classification as having no identified underlying aetiology. In this sensitivity analysis, the respective mean (SD) Vineland ABC scores were 86.9 (18.1) and 79.5 (14.3) ($t_{(97)} = 1.82$, $P = 0.07$; difference 7.4; 95% CI -0.7 to +15.4).

The mean Vineland ABC score in the group of 54 children with an identified underlying aetiology was higher in those allocated vigabatrin, but the difference in scores was not significant (75.9 (11.3) *vs* 70.8 (11.1); $t_{(95)} = 1.36$; $P = 0.18$; difference 5.0 (95% CI -2.3 to +12.4)). This analysis was not of *a priori* interest, but is warranted by the significant interaction term in the ANOVA model.

4.2.1 Investigation of potential bias in timing of Vineland assessments

There is a possibility that differences in Vineland ABC score are due to bias in the timing of these assessments. Since the scores are age standardised by whole months of age, the age standardisation process is relatively more generous to infants who are assessed later in the month of age than to those who are assessed earlier. To investigate whether there were any large differences in the

Table 4.5: Mean (SD) Vineland ABC scores for individual domains by treatment group.

	Hormonal Treatments			Vigabatrin
	Prednisolone	**Tetracosactide**	**Combined**	
Communication	79.4 (10.5)	82.2 (13.3)	80.8 (11.9)	78.9 (9.4)
Living skills	85.0 (11.4)	84.6 (15.4)	84.8 (13.4)	84.7 (9.5)
Socialization	86.6 (16.9)	86.3 (19.5)	86.4 (18.1)	88.1 (16.2)
Motor	77.6 (18.5)	77.9 (20.1)	77.7 (19.1)	76.5 (15.1)

timing of Vineland assessments by treatment group, cases were dichotomised into those whose assessment was performed earlier in the month of age (that is, before the mid-point of the month of age) and those whose assessment was performed later in the month of age. This analysis showed that there was no significant difference in the proportions assessed later in the month of age (hormonal treatment group 20/52 (38%) *vs* vigabatrin group 23/49 (47%); difference −8% (95% CI −28% to +11%); $\chi^2_{(1)} = 0.74$, $P = 0.39$).

4.2.2 Vineland domain scores

Outcomes for the separate Vineland domain scores are shown in table 4.5. Since we had no a priori hypothesis about how these domain scores might be affected by treatments, we did not perform separate statistical tests on these results. There were no striking differences in the domain scores between treatments, but for all three treatments mean scores were lower for the motor domain than for other domains.

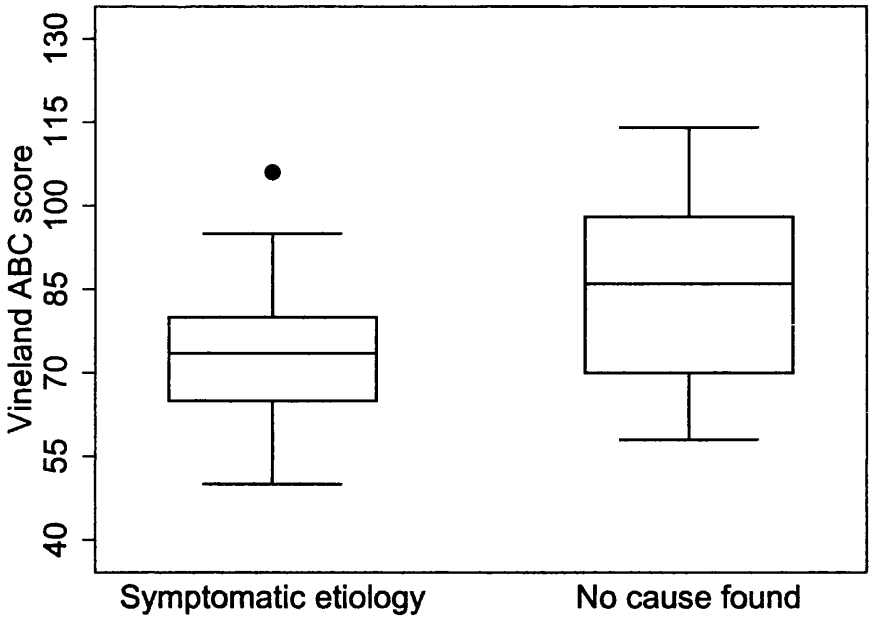

Figure 4.3: Box-whisker plot of Vineland ABC scores by presence or absence of identified underlying aetiology.

4.3 Analysis of potential prognostic factors for neurodevelopment

4.3.1 Neurodevelopmental outcome and underlying aetiology

Mean (SD) Vineland ABC scores were significantly lower in infants with a known underlying aetiology than in infants for whom no underlying cause was found (73.3 (11.4) *vs* 83.8 (16.5), difference 10.5 (95% CI 4.9 to 16.1); $t_{(97)} = 3.70$, $P < 0.001$) (figure 4.3 and table 4.6). Mean (SD) Vineland ABC scores were significantly higher in infants who were primary clinical responders (80.9 (15.0) *vs* 72.7 (13.4), difference 8.2 (95% CI 2.2 to 14.2); $t_{(99)} = 2.68$, $P = 0.009$) (figure 4.4 and table 4.7). These findings invite the question whether the effect of primary clinical response might be on a causal pathway that is initiated by the allocated treatment.

Table 4.6: Vineland ABC score by presence or absence of identified underlying aetiology

	Known aetiology	**No cause found**
Number (%) tested	54 (92)	45 (98)
Mean (SD)	73.3 (11.4)	83.8 (16.5)
Median (IQR)	73.5 (65–80)	86 (70–98)

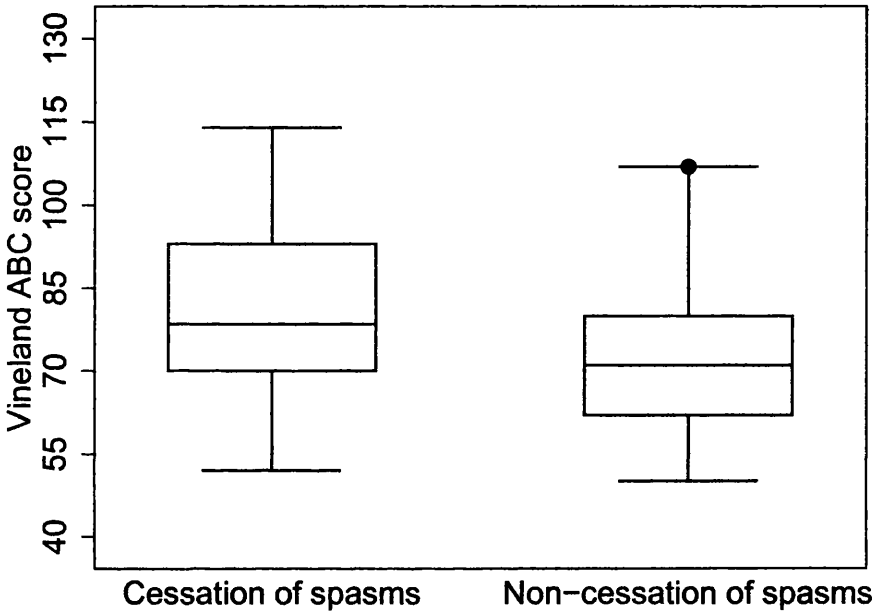

Figure 4.4: Box-whisker plot of Vineland ABC scores by primary clinical response.

Table 4.7: Vineland ABC score by primary clinical response

	Responder	Non-responder
Number (%) tested	66 (97)	35 (90)
Mean (SD)	80.9 (15.0)	72.7 (13.4)
Median (IQR)	78.5 (70–93)	71 (62–86)

Table 4.8: Effects of *lead-time to treatment* upon main outcomes stratified by presence or absence of identified underlying aetiology.

Aetiology	*Lead-time*	Cessation of spasms	Vineland ABC score Mean (SD)
None identified	≤ 1 month	20/25 (80%)[1]	87.0 (15.9)
	>1 month	10/16 (63%)	81.9 (16.1)
Known	≤ 1 month	20/35 (57%)[2]	74.5 (11.3)
	>1 month	11/18 (61%)	71.9 (12.5)
Overall[4]	≤ 1 month	41/61 (67%)[3]	80.3 (14.9)
	>1 month	21/35 (60%)	76.1 (15.1)

[1]*Cessation of spasms*: $\chi^2_{(1)} = 1.52$; $P = 0.22$.
[2]*Cessation of spasms*: $\chi^2_{(1)} = 0.08$; $P = 0.78$.
[3]*Cessation of spasms*: $\chi^2_{(1)} = 0.51$; $P = 0.48$.
[4]Includes 2 cases with aetiological category undetermined.

4.3.2 *Lead-time to treatment* as a potential predictor of neurodevelopmental outcome

Mean (SD) VABS composite scores were not significantly different in those with *lead-time to treatment* of less than 1 month compared with those with *lead-time to treatment* of 1 month or greater (80.3 (14.9) *vs* 76.1 (15.1), difference 4.3 (95% CI −2.2 to +10.7; $t_{89} = 1.32$; $P = 0.19$). Analyses were also made of the subgroups with known aetiology and no identified underlying cause, with *a priori* interest focussed primarily on the group with no identified underlying cause. In neither group was there any significant association between *lead-time to treatment* and *cessation of spasms* or Vineland ABC score (table 4.8). Table 4.9 shows the results of an ANOVA with Vineland ABC score with lead-time and dichotomised etiology and including an interaction term. The interaction term is not significant and lead-time does not independently predict Vineland ABC score.

Table 4.9: Analysis of variance of Vineland ABC score by *lead-time to treatment* and presence or absence of identified underlying aetiology.

Source of variation	**d.f.**	**Mean square**	*F*	*P*
Lead-time	1	333.97	1.73	0.19
Aetiology	1	2720.61	14.1	< 0.001
Lead-time×Aetiology	1	46.66	0.24	0.62
Residual error	85	192.54		

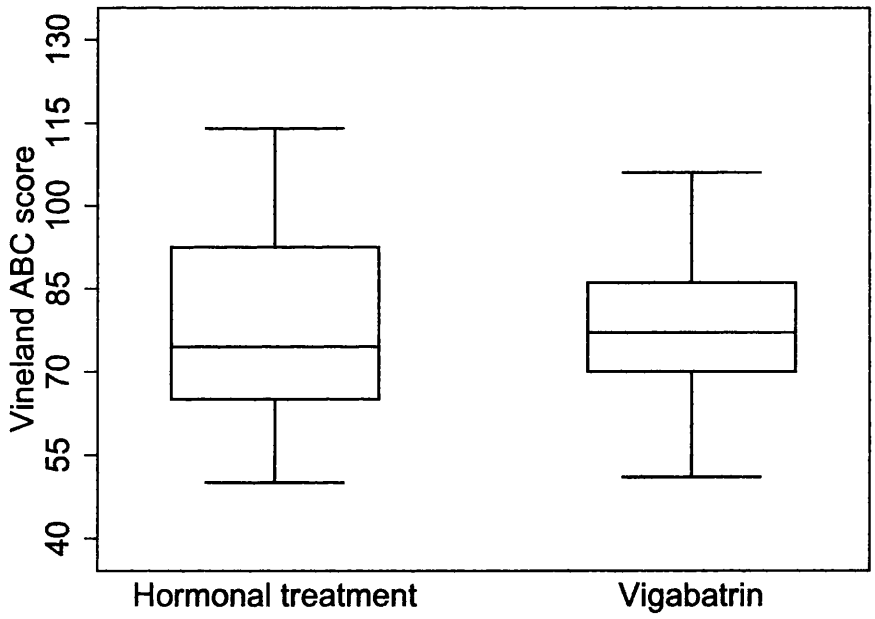

Figure 4.5: Box-whisker plot of Vineland ABC scores by treatment group.

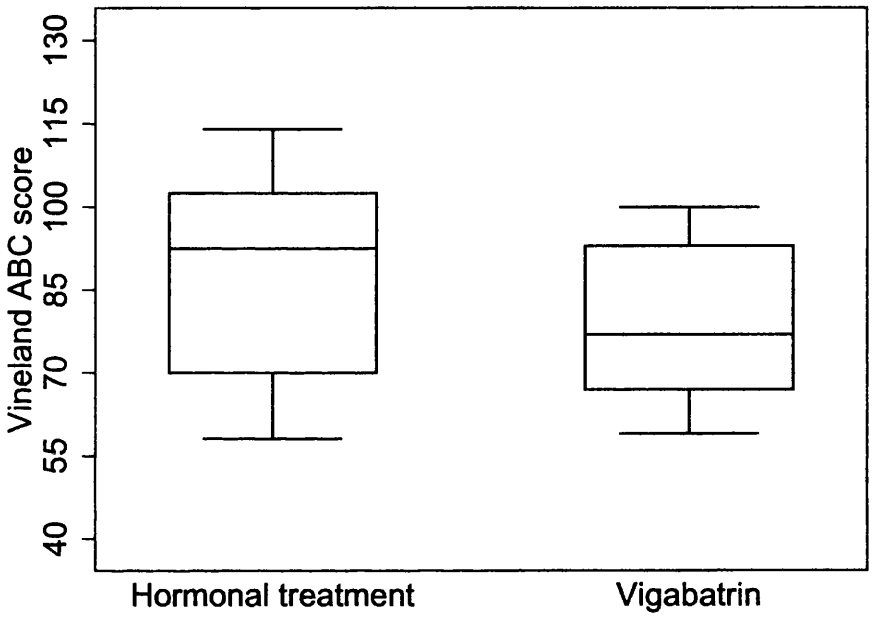

Figure 4.6: Box-whisker plot of Vineland ABC scores by treatment group where no identified underlying aetology.

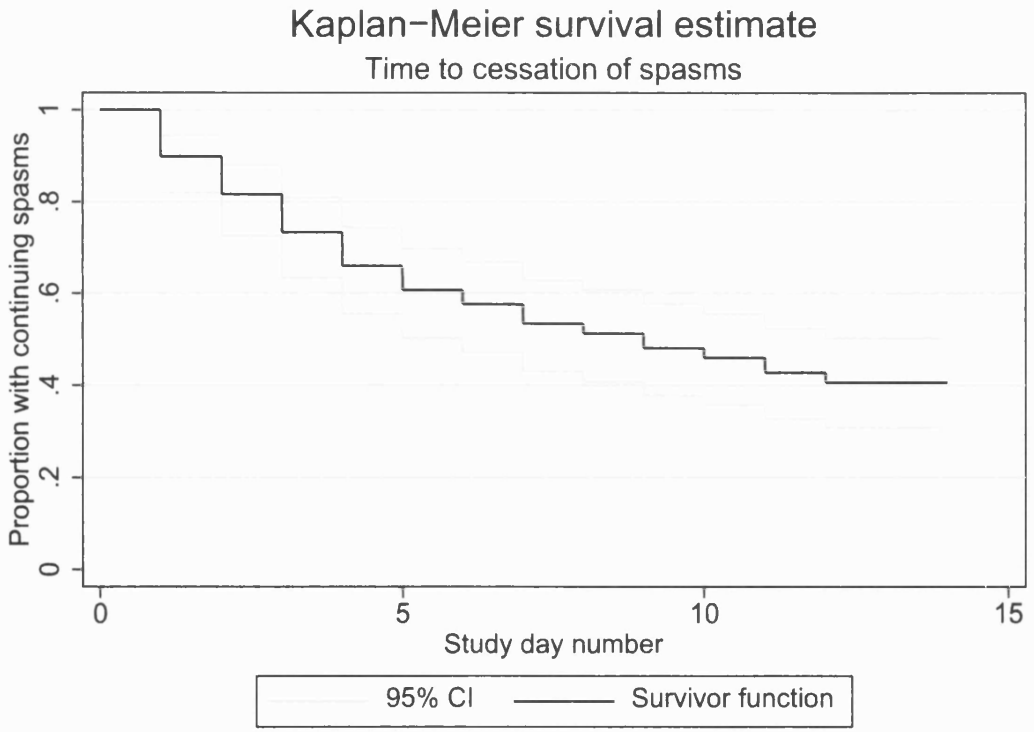

Figure 4.7: Kaplan-Meier survival estimates of time to last reported spasm before end of study day 14 with Greenwood 95% confidence intervals.

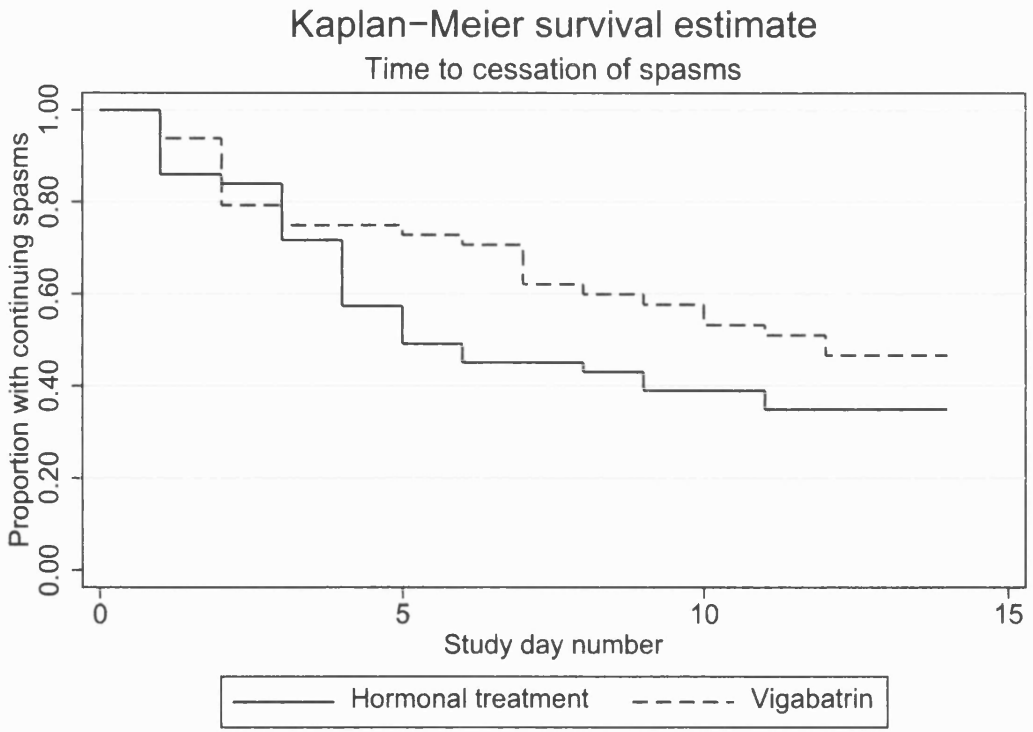

Figure 4.8: Kaplan-Meier survival estimates of time to last reported spasm before study day 14 with hormonal treatments and vigabatrin.

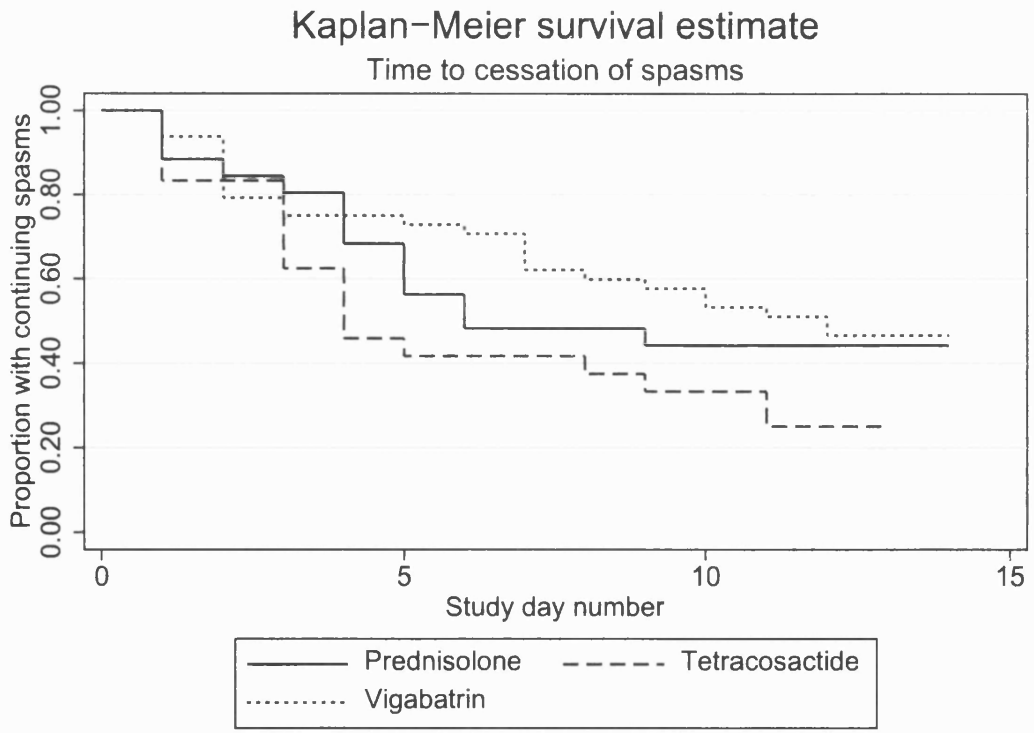

Figure 4.9: Kaplan-Meier survival estimates of time to last reported spasm before study day 14 for all three treatment groups.

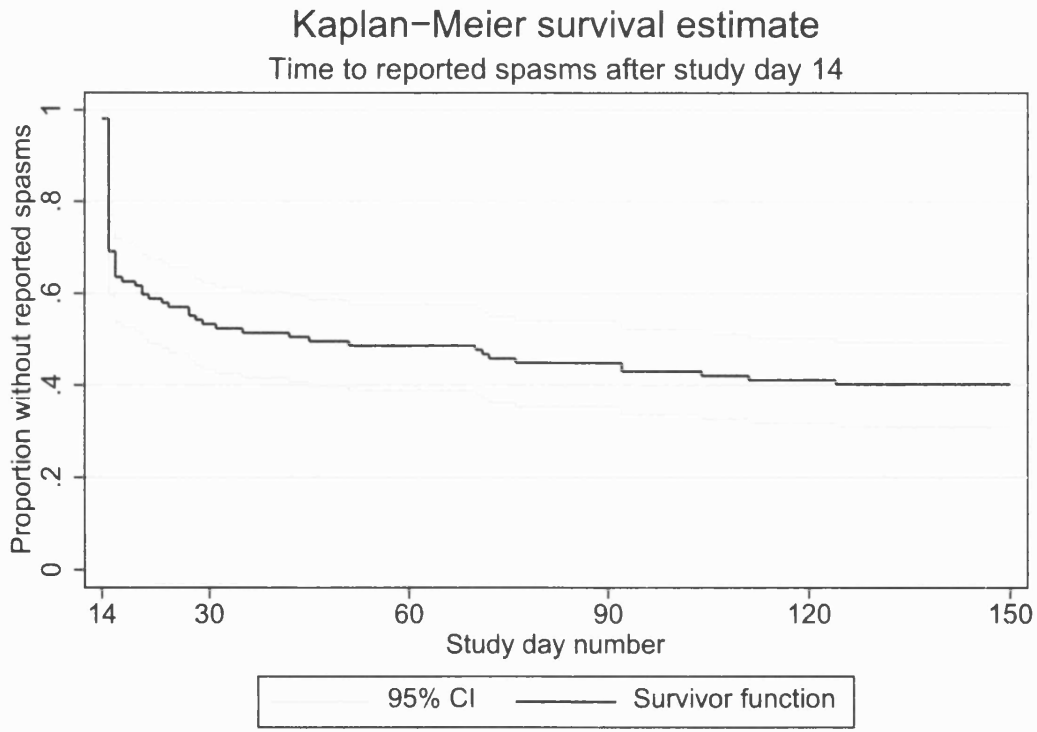

Figure 4.10: Kaplan-Meier survival estimates of time to reported spasms after study day 14 with Greenwood 95% confidence intervals.

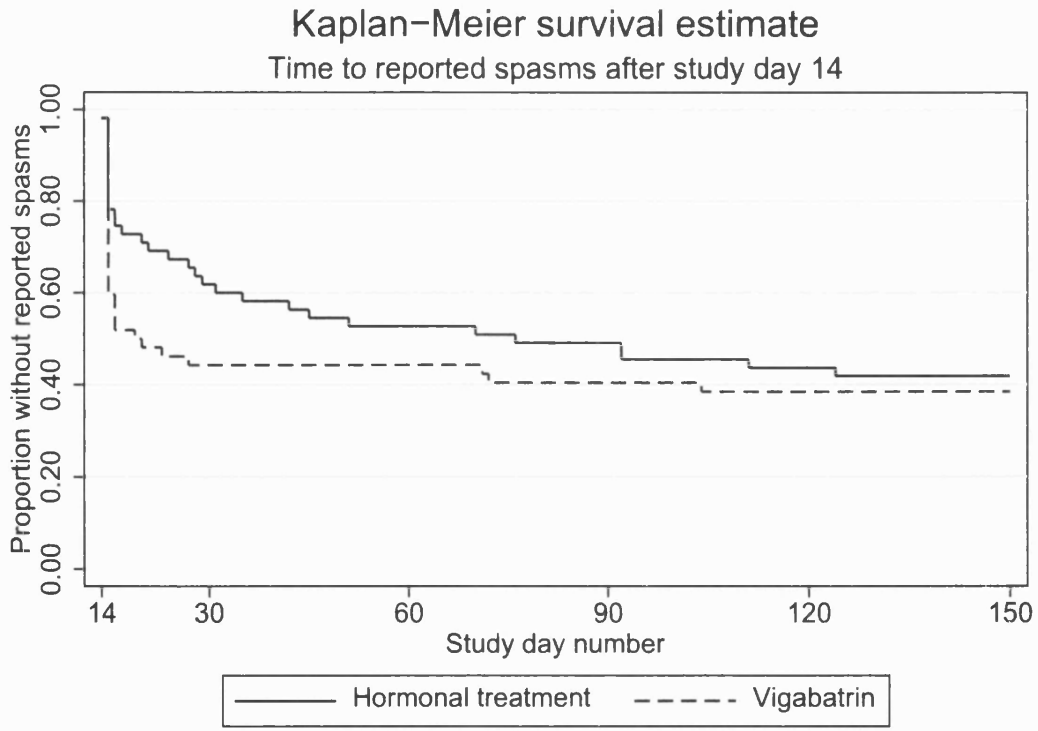

Figure 4.11: Kaplan-Meier survival estimates comparing time to reported spasms after study day 14 with hormonal treatments and vigabatrin.

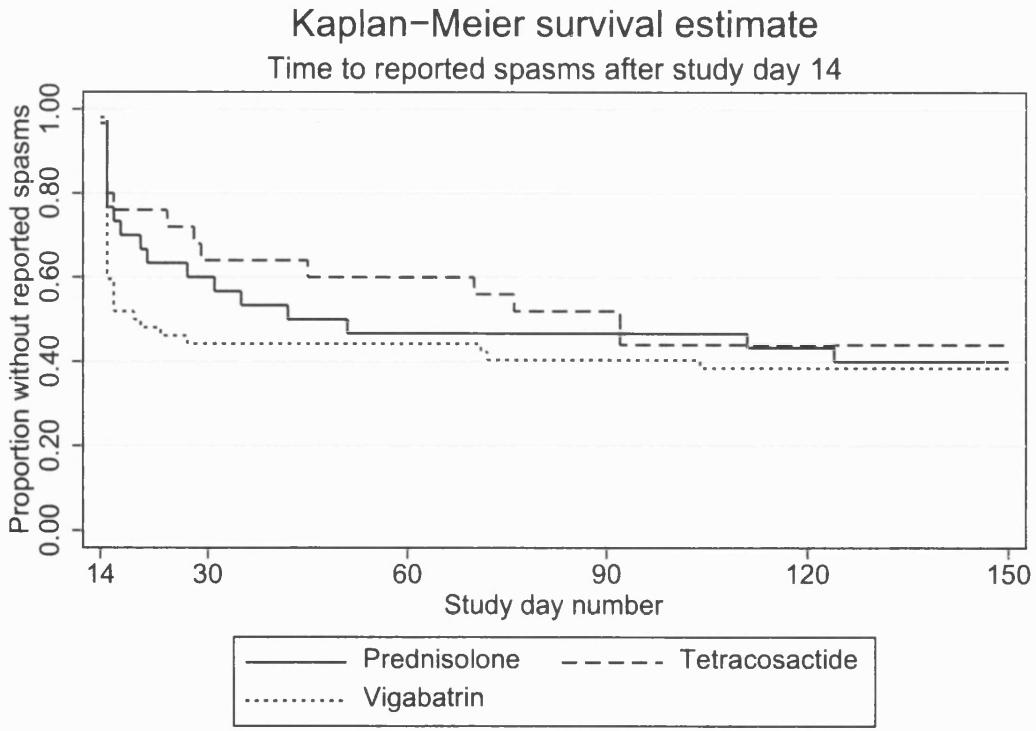

Figure 4.12: Kaplan-Meier survival estimates comparing time to reported spasms after study day 14 in the three study treatment groups.

4.4 Secondary outcomes of the randomised controlled trial

Secondary outcomes are defined in section 26 of the UKISS trial protocol. Item 6 of the stated secondary outcomes, developmental progress at age of 14 months, was later considered to be a main outcome measure, and has already been discussed above. Item 2, partial response defined as reduction in the number of spasms during the first two weeks of treatment, was later considered to be of little or no clinical interest, as is discussed in chapter 5. Item 1, time taken to complete cessation of spasms for a period of 48 hours, is presented below as analysed and presented in the *Lancet* early outcomes paper. Item 3, relapse rates, are discussed below and presented as *relapse-free response*, a variable that was favoured by members of the West Delphi group. Items 4 and 5, presence of other seizure types at age 14 months and resolution of hypsarrhythmia at day 14 of the study, are discussed below.

4.4.1 Relapse and relapse-free response

There was no significant difference between hormonal treatment and vigabatrin groups in the proportions with no reported spasms at final clinical assessment (41/55 (75%) *vs* 39/51 (76%), difference −2% (95% CI −18 to +14%); $\chi^2_{(1)} = 0.05$, $P = 0.82$); and no significant difference in the proportions reported to have *relapse-free response* (that is, *cessation of spasms* at study day 14 and no reported spasms thereafter) (22/55 (40%) *vs* 19/52 (37%), difference 3% (95% CI −18% to +14%); $\chi^2_{(1)} = 0.14$, $P = 0.71$). Thus, although the primary clinical response, *cessation of spasms*, was commoner with hormonal treatments than with vigabatrin, relapse of spasms was commoner with hormonal treatments. The proportions with *relapse-free response* in the three treatment groups were

prednisolone 12/30 (40%), tetracosactide 10/25 (40%), and vigabatrin 19/52 (37%). The relapse outcome could not be reliably determined initially in one infant allocated tetracosactide because the local investigator was unsure how to interpret reports of subtle head movements during one stage of follow-up, but the consensus at the UKISS trial centre was that this case was best classified as having relapse of clinical spasms. Of the 26 infants who were primary clinical responders but relapsed before the final clinical assessment, the earliest relapse occurred before 3 months from study enrolment in all but 2 infants (one infant allocated prednisolone and one allocated vigabatrin). In one infant allocated tetracosactide, the first relapse of spasms occurred while the infant was living abroad and the timing of that relapse could not be reliably determined.

4.4.2 Progression to other seizure types

Seizures other than infantile spasms were reported in the follow-up period to age 12 months in 50 (47%) of infants, with missing data in one case treated with vigabatrin (table 4.10). There was no significant difference between hormonal treatment and vigabatrin groups in the frequency of seizures developing after treatment for infantile spasms (29/55 (53%) vs 21/51 (41%); $\chi^2_{(1)} = 1.42$, $P = 0.23$).

At final clinical assessment, 13/106 (12%) infants were reported as having both spasms and seizures, 13/106 (12%) had reported spasms but no seizures, 20/106 (19%) had reported seizures but no spasms, and 60/106 (57%) had reports of neither spasms nor seizures. Reported absence of both spasms and seizures at the final clinical assessment was commoner with vigabatrin than with hormonal treatments, but this difference was not statistically significant (32/51 (63%) vs 28/55 (51%); $\chi^2_{(1)} = 1.51$, $P = 0.22$).

Table 4.10: Epilepsy outcomes (spasms and other seizure types) reported study day 14 by treatment group and stratified by presence or absence of underlying aetiology and by *cessation of spasms* outcome.

		No spasms No seizures	No spasms Seizures	Spasms No seizures	Spasms Seizures
Aetiology(+)		30	9	2	7
Hormonal treatment	Cessation(+)	16	0	1	2
	Cessation(-)	2	3*	1	1
Vigabatrin	Cessation(+)	8	3*	0	2
	Cessation(-)	4	3	0	2
Aetiology(-)		30	11	11	6
Hormonal treatment	Cessation(+)	8	9	3	1
	Cessation(-)	2	1	1	4
Vigabatrin	Cessation(+)	13	1	1	0
	Cessation(-)	7	0	6	1
Total		60	20	13	13

* Indicates case included in ANOVA model sensitivity analysis.

4.5 Adverse events after study day 14

4.5.1 Deaths occurring after study day 14

Of the five infants who died before the Vineland assessment was performed, three were randomly allocated vigabatrin at the start of the study, and two were allocated prednisolone. One infant (study death 1 below) was allocated vigabatrin, did not have *cessation of spasms*, and later died of an infection while being treated with prednisolone. It is probable that the treatment with prednisolone contributed to this death by suppressing immune responses or masking clinical signs of sepsis, but this is conjectural.

Study death 1

This male infant was enrolled in the study aged 146 days (4.8 months) and was allocated treatment with vigabatrin. There was no *cessation of spasms* and treatment with prednisolone was started on study day 15. He died aged 178 days (5.9 months), 32 days after enrolment in study. The certified cause of death was: Ia. *Staphylococcus aureus* septicaemia.

Study death 2

This male infant was enrolled in the study aged 151 days (almost 5 months) and was allocated treatment with prednisolone. There was *cessation of spasms* but later relapse of spasms, and treatment with vigabatrin and nitrazepam was added. He died at the age of 392 days (12.9 months), 241 days after study enrolment. The certified cause of death was: Ia. Leigh's encephalopathy.

Study death 3

This male infant was enrolled in the study aged 328 days (10.8 months) and was allocated treatment with vigabatrin. There was no *cessation of spasms* and

he later received prednisolone. He died aged 403 days (13.3 months), 75 days after study enrolment. The certified cause of death was: Ia. Encephalopathy; Ib. Primary cerebral atrophy.

Study death 4

This male infant was enrolled in the study aged 348 days (11.4 months), was allocated treatment with vigabatrin, and had *cessation of spasms* without any later relapse of spasms. He did not receive treatment with prednisolone or with any other antiepileptic drugs. He died aged 406 days (13.3 months), 58 days after study enrolment. The certified cause of death was: Ia. Aspiration of vomitus; Ib. Cerebral palsy.

Study death 5

This male infant was enrolled in the study aged 330 days (10.8 months) and allocated treatment with prednisolone. He did not have *cessation of spasms* and later received vigabatrin, carbamazepine, and clobazam. He died aged 471 days (15.5 months), 141 days after study enrolment. The certified cause of death was: Ia: Bronchopneumonia; Ib. Chronic lung disease; II. Microcephaly.

4.5.2 Non-fatal adverse events reported after study day 14

Treatment with randomly allocated medication was reported to be stopped after study day 14 because of adverse effects in 3 cases, all of which received treatment with vigabatrin. In two of these cases the infants were admitted to hospital and treatment was stopped during the hospital admission. The stated symptoms were: (1) Vomiting, weight loss and poor feeding, leading to hospital admission; (2) Excessive drowsiness and continued seizures, leading to

hospital admission; and (3) Irritability, excessive drowsiness, and vomiting. One infant had irritability early during treatment with vigabatrin and later developed excessive drowsiness. Treatment was reduced but continued. One infant in the hormonal treatment group was admitted to hospital on two occasions because of systemic hypertension, and treatment was reduced. None of these infants were reported to have permanent problems as a result of these adverse effects.

Overall, 8 infants (2 allocated hormonal treatments and 6 allocated vigabatrin) were admitted to hospital because of infectious illnesses. One infant was admitted on two occasions because of uncontrolled hypertension. Another infant was admitted to hospital because of a complication attributed to treatment with topiramate. Chickenpox was reported in three infants (2 allocated vigabatrin and 1 allocated tetracosactide depot) during the study period, but none of these was given zoster immunoglobulin.

Seven infants were reported to require admission to hospital because of illnesses attributed to infection. Varicella-zoster infection (chickenpox) was reported in 3 infants (2 allocated vigabatrin and 1 allocated tetracosactide) and 2 infants allocated hormonal treatments were given varicella immunoglobulin because of potential exposure to zoster during the period of likely vulnerability due to hormonal treatment.

Overall, during the period of follow-up to final clinical assessment, 25 study infants were reported to require admission to hospital for reasons that did not require reduction in medication or stopping of medication.

4.6 Summary of later outcomes from UKISS

The most striking finding from the later part of UKISS was that children with no identified underlying cause, in whom we had *a priori* considered that a protective effect of early treatment would be most readily detected, had significantly higher Vineland ABC scores if they had been allocated hormonal treatments rather than vigabatrin. These findings are discussed in chapter 6.

Chapter 5

West Delphi: An International Consensus on Case Definitions, Outcomes and Outcome Measures for Studies of Infantile Spasms

5.1 Overview of West Delphi

Reviewing the evidence for various treatments of infantile spasms led to the realization that there is substantial variation in how outcomes are defined and measured, and also variation in case definitions for children with infantile spasms. Professor John Osborne and I decided that an effective approach to this problem would be to propose a Delphi process aiming to provide an international standard for case definitions and outcome measures for studies of infantile spasms. Our discussion led to the drafting of an initial proposal paper that was presented by Professor Osborne at an *International Symposium on the West Syndrome and Other Infantile Epileptic Encephalopathies* at Tokyo Women's Medical University, Tokyo, Japan: 9–11 February, 2001 [208]. The idea of such

an international consensus was warmly received and several investigators informally agreed to participate in the process. It was informally agreed that a process conducted by email would be efficient and acceptable.

In the discussion following this paper, it was determined that this consensus process would attempt, among other things, to define limits for the EEG features of hypsarrhythmia, including modified or atypical hypsarrhythmia [8, 32, 67]. Many participants were enthusiastic about this proposal, though some thought that, in particular, it would be difficult to achieve a consensus on EEG characteristics. By allusion to William James West and the Delphi process used for consensus elicitation, we decided to refer to this process as *West Delphi*.

It was noted that several ILAE commissions and workshops have proposed definitions and classifications of infantile spasms, and some elements of these are not mutually consistent. For example, proposals from the ILAE Commissions on Classification and Terminology in 1985 and 1989 suggested that cases of infantile spasms should always have onset of symptoms before 12 months of age, whereas a 1991 workshop of the ILAE Commission on Pediatric Epilepsy suggested that infantile spasms "transcends age groups and may occur in infancy or childhood" [28, 34, 35]. Variation in age of onset as a defining criterion alters epidemiological characteristics such as median age at onset of illness, and affects estimates of age-dependent outcomes. In addition to differences in definitions and criteria proposed by the ILAE, there are many other variations in definition, classification, and outcome criteria between published studies.

West Delphi consisted of 6 rounds, though the last two rounds consisted mainly of approval of wording for both the consensus statement and the associated explanatory material that constituted a draft paper to be submitted for publication. There was general consensus within the West Delphi Group that the finally agreed draft should be submitted to the journal *Epilepsia*, and

a version with minor amendments to the one submitted for publication was published in November 2004 [209].

5.2 Methods and conduct of West Delphi

West Delphi was based on the system known as a Delphi process, a method for eliciting expert consensus developed by the RAND Corporation in the early 1950s [210]. In summary, a Delphi process involves isolated experts giving their judgments or opinions to a moderator or facilitator who makes those opinions anonymous and redistributes them to the full group of experts [211]. The process was administered by email and responses were collated by the author of this thesis, who acted as facilitator of the process. Professor Osborne acted as guarantor of the process, but was not aware of the identity of individual respondents and himself participated as a contributor and respondent to questions.

Invitations were sent by email to 133 persons who had published papers as primary authors on infantile spasms during the previous 10 years, or who were known to the author of this thesis or Professor John Osborne to have an interest in infantile spasms. Criteria for selection included presentation at recent symposia on infantile spasms in Seattle, USA and Tokyo, Japan; and publication of a paper on infantile spasms in the previous ten years. Invitations were limited by the ability of the author to locate an email address for the potential participant. Invited persons were asked to forward the email to anyone who they thought would be interested in participating.

The first round included 10 questions with multiple choice format responses (MCQs) that acted as "ice-breaking" questions to stimulate debate and explored some controversial areas. These questions, and those of subsequent rounds, are reproduced in appendix C and responses are reported in this chap-

Table 5.1: Contributors to West Delphi (parentheses indicating responses received too late to be incorporated into feedback).

	Rounds					Authorship
Name	**1**	**2**	**3**	**4**	**5**	
Giuliano Avanzini	*	*				Yes
Tallie Baram		*		*	*	Yes
Rochelle Caplan	*					No
Roberto Caraballo		*	*	*	*	Yes
Kevin Farrell	*	*			*	Yes
Tiziana Granata	*	*		*	*	Yes
Eleanor Hancock		*			*	Yes
Hideji Hattori	*					No
Masatoshi Ito	*	*	*	*	*	Yes
Masayuki Itoh	*					No
Osamu Kanazawa	*					No
Jun Kohyama	*	*		*	*	Yes
Roshan Lal Koul	*	*	*	*	*	Yes
Lee Wei Ling			*			No
Liao Jianxiang	*	*		*	*	Yes
Marissa Lukban	*	*	*			Yes
Tony Marson		*		*	*	Yes
Atsuko Matsuo	*					No
Brain Neville	(*)		*	*	*	Yes
Harry Nomayo	*	*	*	*	*	Yes
Hirokazu Oguni	*	*	*	*	*	Yes
Shunsuke Ohtahara	*	*	*	*	*	Yes
Hian-Tat Ong	*	*	*	*	*	Yes
Marilyn Ortiz	*	*				No
John Osborne	*	*	*	*	*	Yes
Desiderio Pozo Lauzan		*		*	*	Yes
Dietz Rating		(*)	*	*	*	Yes
Aida Salonga	*	*	*		*	Yes
Ingrid Scheffer	*					No
Bernhard Schmitt	*	*	*	*	*	Yes
Ulrich Stephani	(*)	*				No
Yoshihiro Takeuchi	*					No
Malinee Thambyayah	*	*	*	*	*	Yes
Federico Vigevano	*		*	*		Yes
Anannit Visudtibhan	*	*		*	*	Yes
William Whitehouse	*	*	*	*	*	Yes
Virginia Wong	*				*	Yes
Hitoshi Yamamoto	*					No
Hideo Yamanouchi	*	*	*		*	Yes
Chainllie Young	*		*	*	*	Yes
Zhou Zhongshu		*	*			Yes
Total	31	27	20	22	26	30

ter.

In addition to responding to round 1 questions, those agreeing to participate were asked to formulate further questions as a unique contribution to the study. The process made provision for participants to enter after the first round since not all interested persons would necessarily have been contacted in time to respond to round 1. We suggested that, in order to be considered members of the West Delphi Group, participants would need to make contributions to other rounds and to agree the final draft of the proposal. We also suggested that minority and dissenting views would be clearly represented in the final draft, and that the views of contributors would not be censored.

The content and form of subsequent rounds was determined in part by the suggestions of contributors. There was a balance between eliciting quantitative information about the strength of agreements, and eliciting qualitative and creative views on approaching problems of definition, classification, and measurement. The process aimed to focus on aspects of definition and outcome, and to develop proposals that would clarify and simplify study design without introducing unnecessary constraints. Although some participants during the course of the process were keen to make statements relating to evidence for choosing particular first-line treatments, we had decided before the process that we would not attempt to summarise or appraise such information in West Delphi.

In this thesis, reference to questions and statements in the West Delphi rounds are referred to by abbreviations referring to the round and question number such that R1Q5, for example, refers to West Delphi round 1 question 5; and R4S1 to refer to round 4 statement 1.

Table 5.2: Responses to multiple-choice questions in West Delphi round 1.

	Question number									
	1	2	3	4	5	6	7	8	9	10
Response (a)	3	11	2	5	2	2	9	2	3	2
Response (b)	14	8	10	14	10	8	12	1	10	3
Response (c)	7	0	5	4	3	4	6	3	9	5
Response (d)	6	7	11	5	12	15	3	6	7	13
Response (e)	1	5	3	3	4	2	0	12	2	7
Response (f)	-	-	-	-	-	-	-	5	-	1
Response (g)	-	-	-	-	-	-	-	2	-	-
Total	31	31	31	31	31	31	30	31	31	31

Questions appear in appendix C.2 on page 255.

5.3 West Delphi round 1

Invitations to round 1 were sent on 16 January 2002 and the deadline for receipt of responses was 8 February 2002. The ten initial questions covered the following areas: clinical features; restrictions for age at onset; assessing developmental delay; the usefulness of etiologic subgroups; the likelihood of reaching consensus on a definition of hypsarrhythmia; using aggregated data; defining developmental delay; and the interpretation of adverse effects. Round 1 questions are shown in appendix C.2 on page 255, and responses are shown in table 5.2.

There were 31 responses, with contributors from the following countries: Australia, Canada, Germany, Hong Kong, Italy, Japan, Malaysia, Oman, Phillipines, Singapore, Switzerland, Thailand, the United Kingdom, and the United States. One-third of the responses were from Japan and 5 responses were from persons whose invitations were forwarded from other direct invitees. These responses were from Drs Lukban, Granata, Ortiz, Lee, and Stephani. One response was received from four contributors who had discussed West Delphi round 1 questions in the context of a consensus document that they had pre-

pared earlier. This was a German language document prepared by a group referring to itself as the *Königsteiner Kreis*. These comments were treated as a single response in order to avoid undue influence of mutual contributors. One other response was a consensus of opinions from two contributors from one centre (Drs Avanzini and Granata) who were asked to respond individually to subsequent rounds. Three persons responded to Round 1 too late for their responses to be included in the analysis. These were Drs Neville, Caplan, and Liao. The full list of round 1 contributors is shown in table 5.1. This table shows which contributors became final co-authors of the paper and which responses (in parentheses) were received too late to be incorporated into feedback to other contributors.

5.3.1 Round 1 responses to multiple-choice questions

More than half of the participants agreed that the clinical features of infantile spasms were well established (R1Q1) though some contributors included EEG features in their descriptions of what was intended to be restricted to clinical features. One contributor suggested the term *epileptic spasms* to describe the clinical features prior to any consideration of EEG features, and one suggested that clustering of spasms was a necessary feature for the syndrome of infantile spasms.

While a 1-year upper age limit was the most popular single choice for age at onset of spasms (R1Q2) there was relatively little agreement on this point. One third of contributors thought that infantile spasms should be diagnosed only if onset occurs before one year of age, and three fifths thought that a limit of either 1 or 2 years was appropriate. One sixth of contributors thought that there should not be any definitional upper age limit for onset of spasms. One contributor commented that 90% of cases have onset of symptoms by 1 year of age and that including cases with later onset might cause confusion with

other conditions, and another suggested that there is little evidence that infantile spasms occur after 2 years of age. One contributor suggested developing clearer guidelines about adjusting for gestational age, and one comment was that it would be useful to define subgroups for age at onset of spasms, with the terms: *early* (under 3 months of age), *classic* (3 to 12 months), and *late* (over 12 months).

Overall, contributors tended to disagree with the statement (R1Q3) that developmental delay could be reliably timed and classified as preceding onset of spasms. Several participants suggested that age modifies the ability to assess development, with particular difficulties below 3 months of age. Another comment was that the time of onset of spasms cannot be reliably determined, and that apparent developmental delay may in fact be due to unrecognised spasms.

Three fifths of contributors indicated (R1Q4) that they considered aetiological categorisation into the groups *cryptogenic*, *idiopathic*, and *symptomatic*, to be useful, though 1 in 10 disagreed strongly. Some participants commented that this classification is likely to depend upon the sensitivity of the investigative techniques used, suggesting that there would be a trend over successive periods towards a higher proportion being classified as *symptomatic*. One suggestion was that *symptomatic* and *cryptogenic* groups should be collapsed into a single group and contrasted with non-symptomatic cases, since this might better reflect prognosis. One contributor advocated clarity in defining the timing of such classification by distinguishing a categorisation made at the time of diagnosis and initial treatment from categorisation made when the final diagnostic workup has been completed. One third of contributors agreed (R1Q5) that the distinction between *cryptogenic* and *idiopathic* cases can be made readily and clearly, but few had strong responses to this statement and there was a tendency to disagreement with the statement.

One third of contributors thought attempts to identify EEG features that are necessary and sufficient to define hypsarrhythmia (R1Q6) would be too ambitious, but over half thought that it was feasible. One suggestion was that, even if hypsarrhythmia cannot be reliably defined, specific features that are not those of hypsarrhythmia could be used to rule out West syndrome.

The question whether aggregated data from studies, such as meta-analyses, would be likely to help in making treatment decisions (R1Q7) was the only response for which there was greater than two-thirds agreement, and no contributors disagreed strongly. This provided extra motivation for continuing with the attempts at consensus and standardisation since aggregating information from different studies is greatly facilitated by standardised definitions and methodology.

Only one fifth of contributors thought that 7 or fewer days would be a sufficient spasm-free period to define *cessation of spasms* (R1Q8). Two fifths thought that 1 month was an appropriate period, and one-sixth thought that the most appropriate period was two weeks. Fewer than half of contributors definitely agreed with the statement (R1Q9) that the presence of hypertension implies the occurrence of a serious adverse event.

Almost two thirds of contributors thought that developmental assessments (R1Q10) should take place at least as late as 5 years of age, and one-third of those preferred 12 years. Several contributors suggested that an assessment at age 12 years should include items that assess cognitive, social and school functioning. Other contributors were interested in defining a neurodevelopmental, social and educational outcome based upon whether study participants are in mainstream or special schools at the age of 5 years.

5.3.2 Round 1 responses to open questions

In addition to responses to these MCQs, there were many qualitative responses and suggestions that informed the design of questions in subsequent rounds. There were several requests for clearer definitions and consistent usage of the terms *epileptic spasms*, *infantile spasms*, and *West syndrome*, and for criteria to define what constitutes a clinical spasm. There were requests to define the ictal unit, and also to define the relationships between infantile spasms and other syndromes, such as early infantile epileptic encephalopathy (Ohtahara syndrome), Lennox-Gastaut syndrome, and partial epilepsy with periodic spasms (Gobbi syndrome). There were questions about classifying cases with hypsarrhythmia but no clinical spasms, and about classifying cases with hypsarrhythmia and other seizure types. Several contributors asked about retaining or dropping the aetiological category *cryptogenic*. Others asked about retaining or dropping developmental delay at onset as a criterion for West syndrome. One suggestion was that developmental delay might be classified as autistic-type, impaired visual function, or motor.

Several contributors suggested exploring and summarising pathophysiological hypotheses in the hope of formulating a succinct definition of infantile spasms. Other concerns relating to putative mechanisms were about the significance of asymmetrical clinical spasms and of different clinical semiology (flexor, extensor, or mixed spasms). Several contributors were interested in defining a minimal set or an appropriate cascade of investigations for studies of infantile spasms, and ways to link these investigations with etiologic or prognostic classes of infantile spasms. One contributor suggested a minimal set of investigations that would include ictal and interictal standard EEGs (with 12-hour EEG-video preferred) and MRI brain scan. One contributor was interested in prospectively measuring trunk, head and limb movements, and

others were interested in the potential diagnostic role of EMG. One question related to appropriateness of different types of sleep EEG (sleep deprived, sedated, melatonin-induced) and several contributors wished to consider the prognostic value of EEG features.

One suggestion was that there should be 5 ordered categories of outcome, consisting of 3 levels of "success" and two levels of "failure". These suggested categories were: (1) seizure-free and normal EEG; (2) seizure-free, no hypsarrhythmia, and no ictal EEG pattern; (3) no spasms, other seizure type(s) present, and no hypsarrhythmia; (4) seizure-free but persistent hypsarrhythmia or continuous slow spike waves in sleep; and (5) persistent spasms. However, these classes mix clinical and electrographic outcomes and do not necessarily follow a clear ordering. For example, is outcome (4) necessarily a better outcome than outcome (5), or would that depend upon the EEG pattern accompanying the clinical spasms?

Several contributors were interested in recommendations on treatment strategies (specific first-line treatments; doses; add-on treatment; duration of treatment; new AEDs; most appropriate treatments for developing countries). However, these ideas extended beyond those originally intended by the consensus process and were considered likely to considerably extend the time required for the process. One contributor wished to discuss the therapeutic role of pyridoxine, and since pyridoxine has both therapeutic and diagnostic roles, this was considered an appropriate subject for address by West Delphi.

5.4 West Delphi round 2

In round 2, a specific request was made to recruit contributors from Africa, China and South America. However, we had few contacts in those regions and anticipated technical difficulties in delivering email. Also, we encouraged

the participation of investigators from France which, from the time of Gastaut, has had a rich history of contribution to the study of infantile spasms. However, despite directly approaching one investigator and receiving a positive response, we ultimately failed to recruit any regular contributor from France.

Invitations to participate in round 2 of West Delphi were sent on 18 and 20 February 2002, and the deadline for receipt of responses was 11 March 2002. The invitations were accompanied by feedback on responses to round 1. By 11 March, 20 participants had responded. One of these, Dr Rating, did not provide full answers, but suggested that his responses would agree with those of Dr Schmitt. This response was not counted as an individual response, but Dr Rating was added to the respondent list. Three potential participants, one from each of France, the United Kingdom, and the United States, had expressed a keen intention to respond to this round, and two others had requested an extended deadline. On 14 March 2002, potential contributors were told that the deadline had been extended to 25 March 2002. Eight other responses were received, making a total of 27 responses to round 2. Six of these were contributors who had not responded to round 1, one of whom sent a response to round 1 that was too late for analysis, and one other of which was Dr Rating's response (not counted as an independent response). A response from Dr Caraballo (Argentina) was received too late for inclusion in feedback.

5.4.1 Round 2 qualitative responses

The first section of round 2 sought qualitative comments and suggestions in several areas of study design (appendix C.3).

In response to R1Q1, the wording of the overview statement of infantile spasms, 10 contributors made no specific comments. Five said that they agreed with the statement without any amendments, and 6 suggested modifying or dropping the final sentence since they felt there is insufficient evidence that

spasms originate from the subcortex. This area of the statement was the most contentious. One contributor suggested adding the statement: "Psychomotor arrest or retardation usually occur after onset of spasms." Another suggested changing "infantile spasms" to "West syndrome" and changing "epileptic spasms" to "infantile spasms". One suggested that "two years old" should be changed to "one year old", and another suggested that onset should always be below two years of age. With respect to hypsarrhythmia, one respondent suggested qualifying the statement by adding the phrase, "which is usually found between attacks of IS," and also suggested adding the phrase, "and may be found only during sleep."

Suggested terms for the combination of clinical spasms with hypsarrhythmia (R2Q2a) are shown in table 5.4. The mode choice was the term *West syndrome*. Suggested terms for the combination of clinical spasms with epileptiform EEG abnormalities but absence of hypsarrhythmia (R2Q2b) are shown in table 5.5. Suggested terms for clinical spasms with no evidence of EEG abnormality (R2Q2c) are shown in table 5.6, and terms for the scenario of hypsarrhythmia with clinical spasms that occur singly but never in clusters (R2Q2d) are shown in table 5.7. Tables 5.8 and 5.9 respectively show agreement with suggested terms for the scenario of hypsarrhythmia with no observed clinical spasms (R2Q2e) and for cases with clinical spasms that have not yet had an EEG (R2Q2f). Suggested terms for the overall spectrum of conditions with clinical spasms (R2Q2g) are shown in table 5.10. These responses indicated substantial heterogeneity in the terms participants were prepared to use when faced with different clinical scenarios, and also suggested that terms might be used to indicate entirely different scenarios. This illustrated the breadth of the problem relating to definitional terms and acted as additional motivation for the project.

Table 5.3: Responses to multiple-choice questions in West Delphi round 2.

	Question number																			
	8	9	11	12	13	14	15	16	17	18	19	20	21	22	23	26	27	28	29	30
Response (a)	9	8	12	1	1	6	4	3	3	1	1	3	5	8	9	0	0	0	5	6
Response (b)	7	14	5	5	5	5	14	17	5	3	14	13	14	16	12	2	1	0	0	12
Response (c)	2	1	4	4	4	6	6	3	5	5	7	6	4	2	4	1	1	4	4	2
Response (d)	6	0	1	11	11	6	3	2	10	16	4	2	2	0	2	7	2	13	9	4
Response (e)	2	2	4	5	5	3	0	1	4	2	0	1	2	1	0	2	1	4	6	1
Response (f)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	5	12	4	1	-
Response (g)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0	0	1	-	-
Response (h)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	9	8	-	-	-
Total	26	25	26	25	26	26	27	26	27	27	26	25	27	27	27	26	25	26	25	25

Questions appear in appendix C.3.

Table 5.4: Responses to round 2, question 2(a): suggested terms for the combination of clinical spasms with hypsarrhythmia.

Suggested term	***n***
West syndrome[1]	11
Classical West syndrome	2
Infantile spasms	2
Infantile spasms with hypsarrhythmia	2
Epileptic spasms with hypsarrhythmia	2
Classical infantile spasms	2
West syndrome/infantile spasms	1
Typical infantile spasms	1
Clinical spasms with hypsarrhythmia	1

[1]Including West's syndrome ($n = 1$)

Table 5.5: Responses to round 2, question 2(b): suggested terms for the combination of clinical spasms with epileptiform EEG abnormalities but absence of hypsarrhythmia.

Suggested term	***n***
Epileptic spasms	5
Infantile spasms	3
Epileptic spasms without hypsarrhythmia	2
Infantile spasms without hypsarrhythmia	2
Epilepsy with clinical spasms	1
West syndrome without hypsarrhythmia	1
West syndrome	1
Infantile spasms with modified hypsarrhythmia or abnormal EEG	1
Probable infantile spasms	1
Clinical spasms without hypsarrhythmia	1
Myoclonic seizures	1
Other infantile epileptic spasms	1
Clinical spasms with multifocal interictal discharges or burst-suppression	1
Possible infantile spasms	1
Generalized epilepsy with periodic spasms	1

[1]To include more specific EEG description.

The term *West syndrome* was popular as a description for the combination of clinical spasms with hypsarrhythmia. The term *epileptic spasms* was the most popular suggestion for cases with clinical spasms and an epileptiform but non-hypsarrhythmic EEG. There was disagreement about whether apparent spasms in the context of a normal EEG should be called *spasms* or *myoclonus*. Some contributors were prepared to use the term *West syndrome* for cases with no observed clusters of spasms, but rather only single spasms. However, some contributors stated that they would regard absence of clustering as atypical. In the feedback to this round, it was commented that the label *atypical* alone is non-specific, and one might wish to use a term such as *single-spasm variant*. Spasms and IS were equally popular choices to describe the spectrum of conditions with clinical spasms. Several contributors thought that it was not useful to designate a term for cases with clinical spasms but no EEG.

In response to R2Q3, several contributors were keen to retain the terms *idiopathic* and *cryptogenic*, even though there was disagreement about what these terms might refer to. Many contributors considered cases with tuberous sclerosis (TS) to constitute a separate aetiological subgroup. In aggregate, suggestions for main diagnostic subgroups were: tuberous sclerosis, other neurocutaneous conditions, familial and genetic conditions, inborn errors of metabolism, hypoxic-ischemic encephalopathy, cortical dysplasia or other malformations, intrauterine infections. One contributor suggested using a classification system such as the pediatric version of the WHO ICD-10 in order to define a hierarchy of classes.

R2Q4 and R2Q5 were apparently challenging. The most commonly stated necessary feature was high-amplitude slow waves, most often stated with a threshold of 200 μV, sometimes 150 μV. Some suggested that this background should be described as "arrhythmic", "disorganized" or "chaotic", though these descriptions are themselves subjective and require further specification

Table 5.6: Responses to round 2, question 2(c): suggested terms for clinical spasms with no evidence of EEG abnormality.

Suggested term	***n***
Non-epileptic spasms [1]	5
Spasms	3
Infantile spasms	3
Benign myoclonus[2]	2
Spasms, nature undefined	1
Benign spasms	1
Clinical spasms with normal EEG	1
West syndrome	1
WS or IS with hypersynchronous activity on EEG	1
Myoclonic seizures	1
Generalized epilepsy with periodic spasms	1

[1]Including the variants *non-epileptic clinical spasms* and *non-epileptic spasms of infancy.*
[2]Including the variant term *benign myoclonus of infancy.*

Table 5.7: Responses to round 2, question 2(d): suggested terms for the scenario of hypsarrhythmia with clinical spasms that occur singly but never in clusters.

Suggested term	***n***
West syndrome	4
West syndrome – single spasms	4
Atypical IS (or IS variant)	3
Atypical WS (or WS variant)	2
Infantile spasms	1
Single spasms	1
Malignant myoclonic seizures	1

Table 5.8: Responses to round 2, question 2(e): suggested terms for the scenario of hypsarrhythmia with no observed clinical spasms.

Suggested term	***n***
Hypsarrhythmia	5
Non-convulsive hypsarrhythmia	2
Subclinical hypsarrhythmia	1
Isolated hypsarrhythmia	1
Hypsarrhythmia with no observed seizures	1
Hypsarrhythmia without IS (or ES)	1
Patient showing hypsarrhythmia	1
Epilepsy syndrome depending upon semiology	1
No clinical diagnosis	1

Table 5.9: Responses to round 2, question 2(f): suggested terms for cases with clinical spasms that have not yet had an EEG.

Suggested term	***n***
Spasms (or spasms without EEG diagnosis)	4
Still undefined clinical spasms	2
Suspected West syndrome	2
Suspected infantile spasms	1
Infantile spasms	1
Clinical infantile spasms	1
Generalized myoclonic seizures	1

Table 5.10: Responses to round 2, question 2(g): suggested terms for cases with clinical spasms that have not yet had an EEG.

Suggested term	***n***
Spasms (or spasms in childhood)	3
Infantile spasms (or IS NOS)	3
Epilepsy with clinical spasms	2
Clinical IS	1
IS-like	1
Atypical IS	1
Epileptic spasms	1
Spectrum of conditions with IS	1
Entities with generalized myoclonic seizures	1

Table 5.11: Responses to West Delphi round 2, question 25: features considered sufficient to constitute relapse.

Clinical feature	Number agreeing
Spasms occurring in clusters	25
Spasms that do NOT occur in clusters	20
Occurrence of single witnessed spasm	10
Epileptic movements that are not spasms	10
Hypsarrhythmia without clinical seizures	15
Epileptiform EEG but no hypsarrhythmia	2
Abnormal EEG with no epileptiform features	1

or qualification in order to facilitate clear categorisation. The following were regarded as potential necessary features: asynchrony, multifocal spikes and sharp waves occurring randomly from all areas of cerebral cortex (though feedback to this round suggested that this defined feature would exclude hemi-hypsarrhythmia and that the definition might adopt the phrase "randomly from all areas of *affected* cortex" [my emphasis added]); periodicity with alternating low-amplitude periods (as an alternative to a chaotic appearance); greater synchrony, diffuseness, burst-suppression and pseudoperiodicity during sleep; electrodecremental responses; and absence of a sustained posterior rhythm.

Since there was a mode preference in round 1 (12/31 responses, table 5.2) for 28 days as being a standardised duration of spasm freedom to define a primary clinical response *cessation of spasms*, further views were canvassed on this definition (R2Q6). Most contributors agreed that this would be a reliable and useful outcome definition, though further qualification and information were sought by some respondents, such as how this outcome should be backed up with EEG evidence of resolution of hypsarrhythmia and with empirical evidence about relapse frequency after certain periods of spasm freedom. One contributor commented that, compared with studies of other seizures, partic-

ularly in adults, this would be a short duration of seizure freedom.

With respect to R2Q7, suggested specific tests of neurodevelopment were: ADI (Autism Diagnostic Inventory); Bailey test; Beery visual motor integration test; Bender Visual-Motor Gestalt test; Binet test; Conners' questionnaire; Denver Developmental Screening Test version 2; DISCO (Diagnostic Interview for Social and Communication Disorders); Goodman; Griffiths; Kaufmann; Illinois test of psycholinguistic abilities; Leiter International Scales; Motor-free visual perception test; "period of linguistic play"; Rey Complex Figure test; Spreen-Benton Mendilaharsu battery; Vineland Adaptive Behavior Scales; Wechsler, WPPSI (Wechsler Preschool and Primary Scale of Intelligence), and WISC or WISC-R (Wechsler Intelligence Scale for Children (Revised)). One participant suggested that each country might follow its own standard for developmental testing.

5.4.2 Round 2 responses to multiple-choice questions

The second part of round 2 took MCQ format. The questions are shown in appendix C.3 and the responses are shown in tables 5.3 and 5.11.

R2Q10 responses were scored by ranking, with 4 points allocated to the first preference. Three contributors chose (e) and made comments that they did not think an age-related classification was important. In rank order, the choices were: (d) 55.5 points; (b) 51 points; (c) 42.5 points; and (a) 41 points. The scores suggest that no single response was considered substantially more important than the others.

The rank order for response preferences to R2Q24 were: a, f, g, d, c, h, b, e, and the distribution of summed rank scores was: (a) 183; (f) 140; (g) 138.5; (d) 131; (c) 125; (h) 123; (b) 56; (e) 53.5. Eighteen contributors either ranked time to cessation of spasms first (12 responses) or joint first (6 responses). Developmental outcomes ranked higher than serious adverse events. Several par-

ticipants actively disliked time to 50% reduction in ictal units: one participant described it as "inane", and several participants gave it zero stars rather than one.

Responses to R2Q25, which suggested features that might be considered to constitute relapse, are shown in table 5.11. Spasms occurring in clusters was clearly considered to constitute relapse, and more than half of respondents to this round thought that non-clustered spasms and hypsarrhythmia without clinical spasms ought also to be considered sufficient to define one form of relapse.

5.5 West Delphi round 3

In round 3, contributors were invited to respond to 32 statements that represented majority opinions from earlier rounds, and to state whether they agreed with the statement, were unsure about it, or would prefer it to be amended. They were also asked to state whether they thought the statements should be included in the final West Delphi proposal. The first two statements each included a diagram illustrating putative definitional relationships between epileptic spasms, infantile spasms, West syndrome, clustered and non-clustered spasms, and hypsarrhythmia (figures 5.1 and 5.2).

Twenty contributors responded to this round. Round 3 questions were distributed on 13 May 2002 and the deadline for responses was 10 June 2002. Only 8 responses were received by that date, and a further 4 responses were received in the following 4 days. It was decided that an extended time for response was required but that, since round 4 would address issues that were independent in many ways from issues addressed in round 3, further responses to round 3 could be sought while round 4 was being processed.

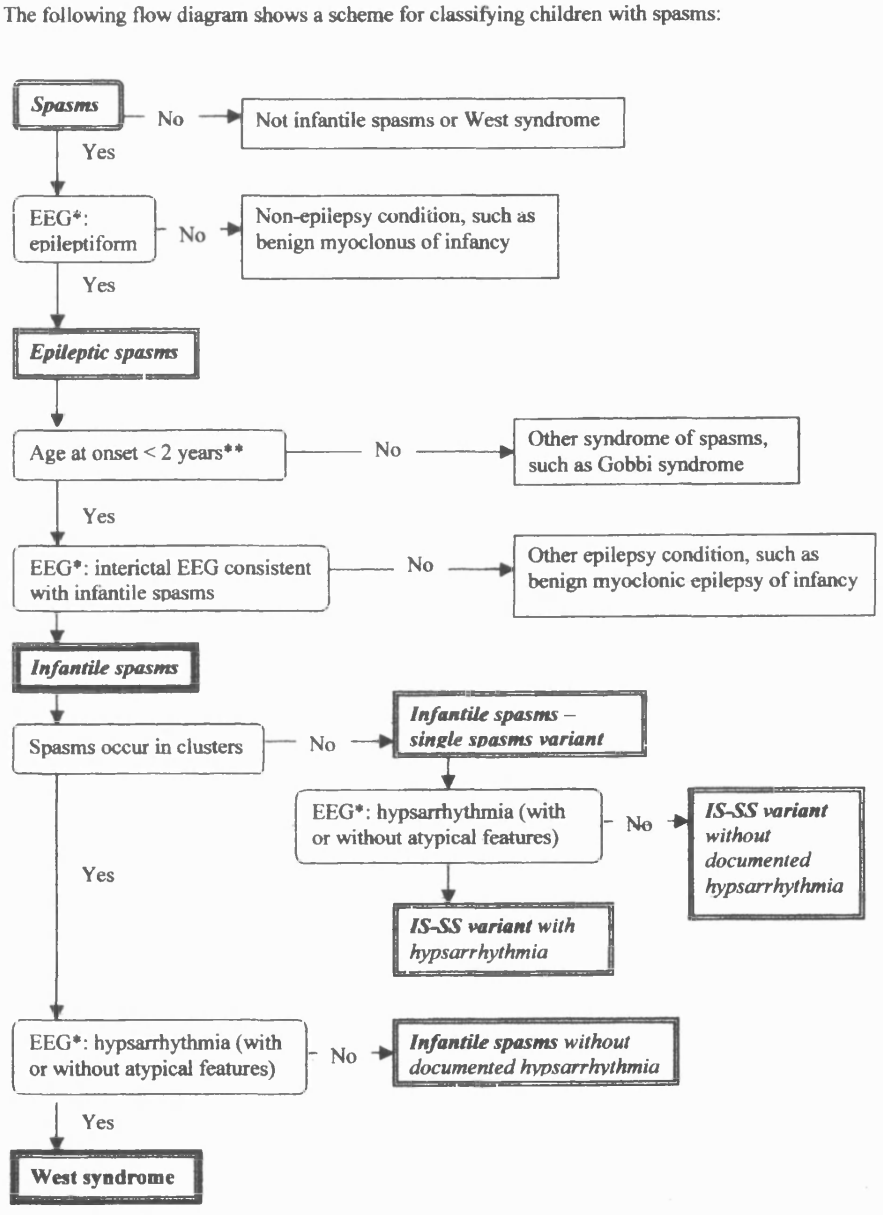

Figure 5.1: Flow diagram showing classification of children with infantile spasms from West Delphi round 3.

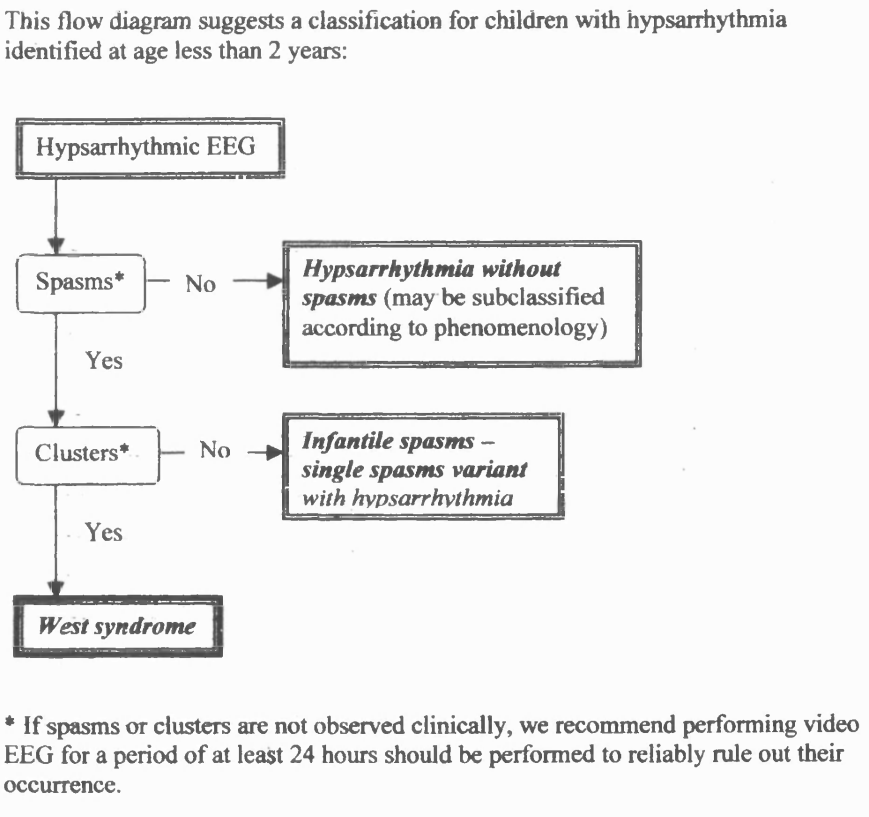

Figure 5.2: Classification of children with hypsarrhythmia without infantile spasms as it appears in West Delphi round 3.

Table 5.12: Responses to West Delphi Round 3.

	Question number															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Response (a)	13	16	14	13	16	15	18	17	17	13	14	16	15	18	15	16
Response (b)	3	5	5	5	2	2	1	0	3	4	5	2	2	1	2	1
Response (c)	4	1	1	2	2	3	1	3	0	3	0	2	3	1	3	3

	Question number															
	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Response (a)	19	15	19	16	14	14	18	18	18	14	14	6	18	18	14	14
Response (b)	1	5	1	4	5	2	2	0	1	2	2	7	0	1	5	3
Response (c)	0	0	0	0	1	4	0	1	0	3	3	6	1	0	0	2

Response (a) = "I generally agree with this statement"
Response (b) = "I am not sure about this statement"
Response (c) = "I disagree with this statement, and my reasons are ..."

Statements appear in appendix C.4.

Questions for this round appear in appendix C.4 and responses are shown in table 5.12. Only three contributors suggested statements to be excluded from the consensus. These statements were round 3 questions 3, 4, 6, 12, 18, 19 (twice), 20 (twice), 21 (twice), 23, 29, and 31. Several contributors suggested that some statements should definitely be included – presumably in order to prevent their exclusion should other contributors suggest that – but did not suggest any exclusions.

5.6 West Delphi round 4

Round 4 presented modified statements, requesting comments on their content and suitability for the proposal. There were 22 responses after extension of the deadline from 30 September to 30 October, 2002. Five contributors were prepared to accept Round 4 statements, without any alterations, as the consensus proposal. The statements associated with round 4 related to the areas shown in table 5.13.

Several contributors wanted a primary outcome that depended in part upon the follow-up EEG findings, and they indicated that they would not be happy to be part of a consensus that did not include this as part of the primary outcome. One contributor commented that, since discussion concerned an epileptic encephalopathy, an EEG response should be a mandatory element of a primary outcome measure. However, some contributors explicitly stated that they prefer clinical outcomes without EEG adjuncts, and it was felt inappropriate to simply drop the clinical primary outcome. This led to the adoption, in round 5 and the final consensus statement, of two primary outcomes: (1) the clinical primary outcome of cessation of spasms as previously defined; and (2) an electroclinical primary outcome that requires cessation of spasms and resolution of hypsarrhythmia.

Table 5.13: Areas covered by statements in West Delphi round 4.

	Area covered by statement
1	Rationale and aim of West Delphi
2	Constitution of the West Delphi Group
3	Definition of infantile spasms
4	Definition of West syndrome
5	Developmental delay at onset of spasms
6	Definition of infantile spasms single-spasm variant (ISSV)
7	Hypsarrhythmia without clinical spasms (HWIS)
8	Relationship between IS, WS, ISSV and HWIS
9	Flow diagrams associated with statement 8
10	Definition of clinical spasms
11	Subtle clinical events
12	Seizure type
13	Clinical spasms, epileptic spasms, and infantile spasms
14	Syndrome classification of infantile spasms
15	Ictal unit of infantile spasms
16	Definition of hypsarrhythmia
17	Modified and atypical hypsarrhythmia
18	Use of Electroencephalograms
19	Aetiological subgroups of infantile spasms
20	Idiopathic infantile spasms
21	Cryptogenic infantile spasms
22	Symptomatic infantile spasms
23	Problems with the terms in statements 20–22
24	Predisposed and non-predisposed subgroups (new terms)
25	Developmental delay at onset of spasms and aetiology
26	Timing classification into aetiological subgroups
27	Classification and reporting of prognostic factors
28	Developmental delay as a prognostic factor
29	Categories of age at onset of spasms
30	Types of intervention (randomised *vs* non-randomised)
31	Duration of treatment
32	Cessation of spasms as primary outcome measure
33	Essential EEG outcome measures
34	Essential adverse event outcome measures
35	Other important outcome measures
36	Time to cessation of spasms
37	Relapse of spasms
38	Pyridoxine-dependent seizures
39	Pyridoxine-responsive seizures
40	Aggregation of data from different studies
41	Areas for future consensus development
42	Summary of the consensus statement

Statements appear in appendix C.5.

Another area for debate was the status of subtle movements and whether they should they be classified as "spasms" for the purposes of enrolment and outcome. One contributor suggested using the terms *infantile spasms* to refer to the seizure type and *West syndrome* to refer to the epilepsy syndrome. Some contributors pointed out that clinical spasms is a pre-axis 1 classification, since the recent ILAE proposal does not formally consider non-epilepsy movement disorders. A central issue was whether the spasms alone can be considered a syndrome (that is, "A distinct group of symptoms or signs which, associated together, form a characteristic clinical picture or entity." [Butterworths Medical Dictionary, 2nd edition]).

There were many other suggestions during this round. Some contributors suggested that the classification *infantile spasms single-spasm variant* (ISSV) with hypsarrhythmia be included as a form of West syndrome rather than as the more generic class of infantile spasms. In contrast, some contributors recommended not including cases with single spasms and without hypsarrhythmia as ISSV. One contributor suggested that the consensus should include a fuller description of the clinical features of infantile spasms that would include mention of clinical features such as flexion, extension, and asymmetry. One contributor requested a fuller description of the EEG features that one might find in modified (atypical) hypsarrhythmia. One suggestion, made by two contributors, was that asymmetric EEG findings predict poorer prognosis, and this might be included as a prognostic factor; and another contributor suggested expanding the description of hypsarrhythmia by discussing the chaotic nature of both frequency and amplitude.

One participant suggested emphasizing the unreliability of timing onset of the disorder by using the term *age when symptom first noticed* in place of the term *age of onset*. Most contributors agree that it is hard to assess developmental delay at onset, but several suggested that unequivocally normal development is

a useful prognostic feature. Since misclassification is a major issue, some participants recommend that studies do not over-emphasize classification based on development at apparent onset of spasms.

One response suggested that, rather than reporting relapse in primary responders, we ought to report the proportion of study subjects with relapse-free response. It is also suggested that we report seizure-free response (distinguishing this from relapse) and that it would be appropriate to standardize these to ages 2 years and 5 years. It was suggested that it is clearer to report time to relapse from the time of randomization or start of treatment than from the time of clinical response.

Several contributors were not convinced that response to pyridoxine is rare, citing personal experience and non-randomised studies. Pyridoxine has been used to treat pyridoxine-dependent seizures and, in its own right and at high doses, as a treatment for infantile spasms. This invited further consideration of the methodological and practical issues associated with using pyridoxine in studies of infantile spasms. At the suggestion of two participants, an opinion was sought from an external expert, Dr Peter Baxter of Sheffield Children's Hospital, Sheffield on the role that might be played by pyridoxine.

Several participants were keen to describe subtle movements associated with appropriate ictal and interictal EEG changes as *subtle spasms*, and several participants put forward a strong argument for accepting subtle spasms as sufficient to constitute a form of relapse.

There was further discussion of aetiological subgroups, with some participants being keen to focus more on specific underlying diagnoses and to move away from subgroup analyses of aetiological subgroups composed of heterogeneous disorders. However, the aetiological subgroups *idiopathic*, *cryptogenic* (or *probably symptomatic*) and *symptomatic* remained popular and it was considered necessary to incorporate these forms of classification in the consensus.

In an attempt to clarify inconsistencies in the use of the terms cryptogenic, idiopathic, and symptomatic, round 4 proposed new terms, *predisposed* and *non-predisposed*. Although some contributors were enthusiastic about these new terms, others disliked the idea of introducing new terms and they were dropped.

One contributor questioned strongly the methodological rigor of using a retrospective etiologic classification, particularly if we wished to perform statistical analyses, suggesting that if we wish to use information about etiologic subgroups to inform future treatment decisions, we ought to use the classification at time of randomization since reclassification of cases will create an information bias. However, it was also considered useful to use information about cases when a final underlying diagnosis and presumed cause has been more specifically determined in order to provide prognostic information relating to specific underlying causes.

5.7 West Delphi rounds 5 and 6

Round 5 consisted of a draft paper for submission as a final proposal from the West Delphi Group. These statements were similar to the final consensus statement apart from some details discussed below, and they are not reproduced independently in this thesis. Round 5 included 42 statements and a cover letter outlining areas of incomplete agreement and contention. The areas covered by these statements and the number of comments in response to each of these statements are shown in table 5.14.

In response to these comments, which were made by 11 contributors, and after discussion with Professor Osborne that did not reveal the identity of the individual contributors, the author corresponded directly with those contributors to clarify the remaining points of incomplete agreement. Contributors

Table 5.14: Areas covered by statements in West Delphi round 5.

	Area covered by statement	**Number of comments**
1	Rationale and aim of West Delphi	0
2	Definition of infantile spasms	2
3	Definition of West syndrome	0
4	Developmental delay at onset of spasms	1
5	Definition of infantile spasms single-spasm variant (ISSV)	5
6	Hypsarrhythmia without clinical spasms (HWIS)	0
7	Subtle spasms and relapse	5
8	Relationship between IS, WS, ISSV and HWIS	2
9	Flow diagrams associated with statement 8	3
10	Definition of clinical spasms	0
11	Subtle spasms	3
12	Epileptic spasms as seizure type	0
13	Clinical spasms, epileptic spasms, and infantile spasms	0
14	Syndrome classification of infantile spasms	1
15	Ictal unit of infantile spasms	2
16	Definition of hypsarrhythmia	3
17	Modified and atypical hypsarrhythmia	1
18	Use of Electroencephalograms	3
19	Aetiological subgroups of infantile spasms	3
20	Idiopathic infantile spasms	2
21	Cryptogenic infantile spasms	5
22	Symptomatic infantile spasms	4
23	Problems with the terms in statements 20–22	1
24	Timing of aetiological classification	2
25	Specific aetiological categories (referenced to appendix)	1
26	Reporting of baseline characteristics	1
27	Age categories for time at onset of spasms	1
28	Duration of a sufficient therapeutic trial	1
29	Primary clinical outcome	0
30	Timing of EEG investigations	1
31	Resolution of hypsarrhythmia *vs* normalisation of EEG	1
32	Role of sleep EEG and 24-hour video-EEG	4
33	Primary electroclinical outcome	2
34	Roles of primary clinical and electroclinical outcomes	0
35	Reporting of deaths occurring during study period	0
36	Suggested outcome measures	3
37	Multiple subgroup analyses	0
38	Reporting time to cessation of spasms	1
39	Clinical relapse of spasms	0
40	Pyridoxine-dependent seizures	3
41	Pyridoxine as an adjunct treatment	3
42	Areas for future consensus development	0

Statements discussed in section 5.7.

who still wished to amend the consensus statements were were asked to respond within two weeks if they felt that we had not given sufficient or appropriate consideration to their suggestions, or if we had misunderstood what they were trying to suggest. The collected and anonymised responses, with some explanation and clarification by the author, were then sent to all contributors.

West Delphi round 6 consisted essentially of seeking written approval and any final comments from the contributors in order to submit the paper for publication. There were no major dissenting views, though it was appreciated by many contributors that, for the sake of consensus, several of the expressed proposals – and particularly definitions that required some arbitrary limits – would not have been their individual first choices. The final consensus statement was published in *Epilepsia* and is reproduced in appendix D. The final suggested system of aetiological classification is shown in table 5.15.

Table 5.15: West Delphi classification of aetiology.

Aetiological category	ICD-10 code
Neoplasm	
Malignant	C71
Benign	D33
Endocrine/metabolic(not transient neonatal)	
Hypoglycaemia	E16
Classical phenylketonuria	E70
Organic acidurias	E71
Aminoacidurias	E72
Enzyme deficiencies (e.g. Krabbe, Leigh, biotinidase)	
Nervous system (not perinatal)	
Meningitis	G01-02
Encephalitis	G05
Cerebral abscess	G07
Cerebral palsy (unknown cause only)	G80-83
Porencephaly	G93
Other (if not classified elsewhere; e.g. leukomalacia)	
Cerebrovascular disease (not perinatal)	
Cerebral haemorrhage	I60-62
Cerebral infarct or stroke	I63-64
Perinatal	
Maternal factors (e.g. drug abuse)	P04
Birth trauma (including HIE if due to trauma)	P10-11
Intrauterine asphyxia (HIE)	P20-21
Infections (e.g. meningitis, toxoplasma, CMV, herpes)	P35-36
Intracranial nontraumatic haemorrhage	
Transient endocrine or metabolic neonatal disease	P70-74
Other (e.g. PVH/PVL) secondary to preterm injury	P91
Hypoxic-ischaemic injury of uncertain cause	
Congenital (non-chromosomal)	
Agenesis of the corpus callosum	Q04
Agyria/polygyria	
Cortical dysplasia	
Heterotopia	
Holoprosencephaly	
Hydrocephalus	
Microcephaly	Q02
Congenital (specified disease)	
Incontinentia pigmenti	Q82
Neurofibromatosis	Q85
Tuberous sclerosis	Q85
Hypomelanosis of Ito	Q92
Congenital (chromosomal)	
Down syndrome	Q90
Other: please specify	

HIE = Hypoxic-ischaemic encephalopathy.
PVH/PVL = Periventricular haemorrhage and/or leukomalacia.

Chapter 6

Discussion

6.1 Summary of main findings in this thesis

Analysis of the primary outcome of UKISS, *cessation of spasms*, showed a statistically significant difference between hormonal treatments (prednisolone or tetracosactide) and vigabatrin. The 95% confidence range for the difference in effects (1% to 36%) provides evidence against vigabatrin being a superior treatment with respect to this outcome measure, but it does not provide unequivocal evidence that hormonal treatments are superior. The secondary analysis, comparing prednisolone against tetracosactide, showed no significant differences in treatment effect, and in fact there was very little difference in the effect estimates for these two treatments.

Vineland Adaptive Behavior Composite scores at age 14 months were not significantly different in the hormonal treatment and vigabatrin groups, but the scores were significantly higher in infants allocated hormonal treatments in the subgroup of infants who had no identified underlying aetiology. However, this finding was borderline rather than robust, and a sensitivity analysis that included two cases who were not reliably classified into aetiological categories because of absent neuroimaging information, resulted in the difference

in Vineland ABC score being no longer significantly different between the two groups.

The West Delphi consensus process led to the development of a consensus statement that was agreed by 31 participants from 15 countries. There was clear agreement on many aspects of study design that have potential to improve and standardise future studies of infantile spasms. There was incomplete consensus and a limited statement on some aspects of study design relating to infantile spasms, and in particular on the issue of definitions for EEG criteria.

6.2 Discussion of UKISS

In the mid-1990s, the first-line treatment of infantile spasms in the United States was ACTH, the most popular regimen being 40 iu/day for 1–2 months [212]. In Japan, ACTH was generally used in smaller doses and as second-line or third-line treatment of infantile spasms, the most popular first-line treatment being pyridoxal phosphate [213]. Neither the United States nor Japan have licensed vigabatrin, but vigabatrin has found popular use in Europe. Indeed, even during the course of enrolment in UKISS, several letters were published in the BMJ relating to recommended use of vigabatrin as a first-line, and indeed *first-choice*, treatment of infantile spasms, with responses from the UKISS trial steering committee that aimed to justify continued enrolment of cases in a randomised trial.

Since the UKISS study started to enrol participants, there has been a published Cochrane Review on treatment of infantile spasms [214, 215] and another review using, to some degree, an evidence-based methodology [216]. In addition, the American Academy of Neurology (AAN) and the Child Neurology Society (CNS) have published recommendations, termed a "practice

parameter", on the treatment of infantile spasms. Its summary states that:

> Adrenocorticotropic hormone (ACTH) is probably effective for the short-term treatment of infantile spasms, but there is insufficient evidence to recommend the optimum dosage and duration of treatment. There is insufficient evidence to determine whether oral corticosteroids are effective. Vigabatrin is possibly effective for the short-term treatment of infantile spasm and is possibly also effective for children with tuberous sclerosis. Concerns about retinal toxicity suggest that serial ophthalmologic screening is required in patients on vigabatrin; however, the data are insufficient to make recommendations regarding the frequency or type of screening. There is insufficient evidence to recommend any other treatment of infantile spasms. There is insufficient evidence to conclude that successful treatment of infantile spasms improves the long-term prognosis.

And its final conclusion seems very conservative indeed: "ACTH is probably an effective agent in the short-term treatment of infantile spasms. Vigabatrin is possibly effective." This practice parameter was published before the results of UKISS, and it is possible that our findings will lead to changes when a similar practice parameter is next produced. For example, a new practice parameter might interpret UKISS findings as evidence that high-dose oral steroids have similar effect to intramuscular ACTH preparations; or it might suggest that there is now cumulative evidence that, in non-TSC cases of infantile spasms, hormonal treatments have proven superiority over vigabatrin as first-line treatment with respect to early cessation of spasms, and possibly with respect to neurodevelopmental outcomes in cases with no identified underlying aetiology. However, the generally conservative tone of the earlier recommendation would make such a strong interpretation unlikely.

6.2.1 Comparison of UKISS findings with other studies of hormonal treatments against vigabatrin

The difference in the proportions with *cessation of spasms* in hormonal treatment and vigabatrin groups was similar to those found in the smaller study by Vigevano and Cilio, although that study was smaller and the difference was not statistically significant. As discussed in section 1.12.2 and in the trial steering committee's earlier letter to the *BMJ*, the proportions with cessation of spasms before 20 days were 14/19 (74%) in the ACTH-treated group and 11/23 (48%) in the vigabatrin-treated group, a difference in treatment effect of 26%, with a 95% confidence interval for that difference from -3% to 54% [188].

Cossette *et al* published a retrospective study of 42 children with infantile spasms with some excluded cases. They reported an initial response to ACTH in 18/21 (86%) infants, and to vigabatrin in 16/21 (76%), with relapse in 4/18 and 0/21 infants in the respective treatment groups [217]. An erratum to this paper was published after the author of this thesis and Dr F.J.K. O'Callaghan, both members of the UKISS trial steering committee, sent a letter to the editor of *Neurology*. The editor of *Neurology* did not wish to publish the criticism that reassurance about absence of visual impairment in children of this age was invalid, though did not state a compelling reason for this. He did agree to publish an erratum relating to the repeated statistical testing without an appropriately more conservative *P*-value, but he suggested that associating oneself with an erratum, even as though the researcher bringing the error to light, was unwise, and we agreed not to be acknowledged in this respect.

In the erratum, Cossette *et al* acknowledged that the statistical method used to evaluate the differences between both groups should have been the Fisher exact test rather than the chi-square test (owing to the small number of individuals in certain groups). Hence, the differences in relapse rates were not

statistically significant, with P values at 3, 6, and 12 months of 0.11, 0.10, and 0.17, respectively. The erratum also stated that the authors of the paper by Cossette *et al* did not suggest that vigabatrin is superior to ACTH, but that it is "their drug of first choice because of its more favorable side-effect profile when used over a 12-month period for the control of infantile spasms."

6.2.2 Comparison of UKISS findings with other studies of vigabatrin

Early reports of add-on treatment suggested that vigabatrin is more effective in symptomatic infantile spasms. Aicardi *et al* retrospectively reviewed 250 cases of infantile spasms, 196 of whom were considered to have "classic IS", and reported initial clinical response in 131/192 (68%) of cases with relapse in 28/131 (21%) [167, 168]. However, the primary clinical response used in these reports was not clearly defined.

Several later studies have reported vigabatrin to be generally more effective treatments of non-symptomatic than of symptomatic infantile spasms. Two larger non-randomised studies have reported response in 24/82 (29%) and 15/39 (38%) of symptomatic cases, and 21/34 (62%) and 22/31 (71%) of non-symptomatic cases [78, 218]. Wohlrab *et al* reported initial response, defined as resolution of both spasms and hypsarrhythmia, to vigabatrin treatment in 14/28 (50%) of infants [219]. There were reported to be no relapses in this treatment group. This same research group has reported four children with Angelman syndrome who showed worsening of seizures within several days of reaching maximal dose treatment with vigabatrin [220]. Granström *et al* reported response in 11/42 (26%) of infants given vigabatrin, with one case later relapsing [221].

Symptomatic cases whose underlying cause is tuberous sclerosis seem to

respond better to treatment with vigabatrin than symptomatic cases with other underlying causes. However, one group of investigators have reported a high rate of relapse in cases with tuberous sclerosis whose first-line treatment was vigabatrin alone, and they excluded children with tuberous sclerosis from a later study of vigabatrin monotherapy because of this relatively high risk of relapse of spasms [218].

Two randomised studies of vigabatrin for the treatment of infantile spasms were reported after UKISS started to enrol participants. Appleton et al reported a placebo-controlled trial of vigabatrin, with the primary clinical outcome being absence of reported spasms on study day 5 [95]. And Elterman *et al* reported outcomes on 142 infants treated with vigabatrin at either high-dose (100–148 mg/kg/day) or low-dose (18–36 mg/kg/day) [222].

Appleton *et al* reported a significant difference in the outcome *reduction in spasms* compared with baseline: 78% (95% CI 55% to 89%) for vigabatrin compared with 26% (-56% to 65%) for placebo, with a reported *P*-value of 0.02. However, cessation of spasms was reported in 7/20 (35%) of infants allocated vigabatrin compared with 2/20 (10%) of those allocated placebo, a difference that is not statistically significant. The *P*-value cited for this difference in proportions with reported cessation of spasms is the value obtained from a one-sided Fisher exact test, but a two-sided test would arguably be more appropriate – and is conventional in clinical studies – and this yields $P = 0.13$. The chi-square value is also insignificant: $P = 0.06$.

The infants in the study of Elterman *et al* were selected from 179 infants allocated randomised treatment with "high-dose" or "low-dose" vigabatrin. The *high-dose* regimen would be considered a standard regimen in Europe. Of these infants, 167 received vigabatrin, and outcomes were known 142. Six infants were given an incorrect initial dose of vigabatrin, 3 infants in each of the high-dose and low-dose groups. Analysis was made by intention to treat,

with the proportion responding to high-dose vigabatrin, 24/67 (36%), being lower than that in UKISS but similar to that in the study of Appleton *et al*; and with reported responses in the low-dose vigabatrin group in 8/75 (11%). This difference is statistically significant ($\chi^2(1) = 12.8, P < 0.001$).

A published criticism of this paper was made by members of the UKISS steering committee [223]. This response credited the study as being a significant advance in the study of infantile spasms, being substantial in size, clearly defining response and relapse both clinically and electrographically, and using survival analysis (actuarial) techniques. However, the trial steering committee criticised several aspects of the analysis performed by Elterman *et al.* Outcomes were reported on only 142/179 (70%) of cases, with 16 missing observations from those allocated high-dose vigabatrin and 9 observations missing from those allocated the low-dose regimen. In a further 10 cases, it was not known which dose had been allocated, and 2 cases were known not to have received the randomly allocated treatment. The number of missing observations (37) is substantial compared with the overall number of responders, which was 32, and certainly large enough to introduce substantial bias. A sensitivity analysis was not performed. Of those with an underlying diagnosis of tuberous sclerosis, 13/25 (52%) had cessation of spasms, but it was not clear from the paper how many responders were in high-dose or low-dose groups. Only 19/117 (16%) of cases with other underlying aetiologies, either identified or unidentified in the paper, responded to high-dose or low-dose regimens. The reported responses over the 3-month period of follow-up could be due to concomitant treatments other than vigabatrin, about which no information was included in the paper. The study claimed to confirm both safety and efficacy of treatment with vigabatrin, whereas the view of the UKISS steering committee was that there are no reliably validated methods for assessing visual field losses, which are probably the most likely serious adverse effect, and that the

safety of vigabatrin cannot be confirmed in this respect.

6.2.3 Comparison of UKISS findings with other studies of prednisolone against tetracosactide

The comparison of prednisolone against tetracosactide in UKISS was substantially underpowered. Even if 250 children had been recruited, as had been intended in the study protocol, the power to detect a significant difference between these two treatment arms would have been only 55%. However, the point estimates for the treatment effects measured as *cessation of spasms*, 70% and 76% for prednisolone and tetracosactide respectively, are very similar and it seems unlikely that, with these particular treatment regimens, a significant difference would have been found if the study had recruited the originally planned number of participants. In addition, the two cases that were randomly allocated tetracosactide but in fact received prednisolone both responded with *cessation of spasms*, such that an analysis by treatment actually received rather than by intention to treat gives an even smaller difference in effects of 23/32 (72%) for prednisolone versus 17/23 (74%) for tetracosactide.

No previous studies have compared prednisolone against tetracosactide in the treatment of infantile spasms, but other studies have compared other ACTH and corticosteroid regimens, as discussed in section 1.12.1. The study of Baram *et al* showed a significantly higher response to treatment with ACTH at a dose of 150 mg/m^2/day than with prednisolone at a dose of 2 mg/kg/day [182]. In the ACTH-treated group, 13/15 had cessation of spasms and resolution of hypsarrhythmia, and one of the two non-responders had cessation of spasms but unresolved hypsarrhythmia. In the prednisone-treated group, only 4/14 infants had both cessation of seizures and resolution of hypsarrhythmia at 14 days. The differences in primary response are statistically significantly

($\chi^2_{(1)} = 10.1$, $P < 0.002$). Although there was a good response to treatment with ACTH in those participants who failed initial treatment with prednisone (8/9 had cessation of spasms and resolution of hypsarrhythmia within 14 days compared with one of two who had changed to treatment with prednisone) no clear conclusion can be drawn from these cases that had received a secondary treatment since the numbers are small, there was no washout period before starting the second treatment, and the effects of hormonal treatment may be delayed. However, the dose of prednisolone used in UKISS was substantially higher than that used for prednisone in the study of Baram *et al*, and one *a priori* hypothesis in UKISS was that this relatively higher dosage regimen would better mimic the effects of potent adrenocorticotropic activity and lead to a reduction in differences in effect. The study of Baram *et al* concluded that high-dose ACTH is a better treatment than "standard" doses of prednisone. It also discussed the potentially low value of assessing developmental outcome with this study design, in which non-responding participants were exposed to the alternative treatment, but this criticism of measuring neurodevelopmental outcomes is not fully justified (see section 6.2.4).

The study of Hrachovy *et al* used a smaller dosage regimen of ACTH and was relatively underpowered, but like UKISS it did not find any significant difference between ACTH and corticosteroid regimens [93]. The primary outcome was cessation of spasms and resolution of the EEG pattern of hypsarrhythmia at 14 days. The numbers responding were lower than in the earlier studies: 5/12 in the ACTH group and 4/12 in the prednisone group. After a further 4 weeks of failed treatment and a one-week drug washout period, non-responders were treated with the alternative drug. At that time, 4/8 responded to ACTH, and 3/7 responded to prednisone. Relapse occurred in 5 participants, 3 in the ACTH-treated group and 2 in the prednisone-treated group. All of these responded to a further two-week course of treatment with

the original drug. Hypertension was not clearly defined, but was reported to occur in 4 participants treated with both trial drugs, and in 2 participants who had been treated with prednisolone only.

As discussed in section 1.12.1, the study of Snead *et al* did not have randomly allocated treatments, blinding, or a clear definition for the primary clinical outcome. Of the 116 children in the study, 52 (45%) had infantile spasms with hypsarrhythmia and 30 (26%) were described as having "infantile spasms – myoclonic seizures [without] hypsarrhythmia." In the former group (infantile spasms with hypsarrhythmia) seizure control was reported in 30/30 (100%) of infants treated with ACTH and 13/22 (59%) of those treated with prednisone ($\chi^2_{(1)} = 14.8$; $P < 0.001$). The proportions with seizure control in the latter group (infantile spasms or myoclonic seizures without hypsarrhythmia) were 13/16 (81%) with ACTH and 0/14 (0%) with prednisolone ($\chi^2_{(1)} = 20.1$; $P < 0.001$). These are substantial differences, despite the relatively higher dosage regimen of prednisone compared with previous studies. Also, the response rates to ACTH (100% and 81% in the hypsarrhythmia present and absent groups respectively) are high compared with other studies. The findings are not consistent with those of UKISS. Any reasons for the different findings in this study are speculative, but it is possible that there was substantial selection bias, or simply that the differences and unusually high response rates to ACTH treatment are due to chance.

6.2.4 Neurodevelopmental outcomes

UKISS is the first randomised controlled trial of infantile spasms to systematically measure neurodevelopmental outcomes. One benefit of Vineland Adaptive Behavior Scales is that the interview can be performed by telephone by a trained researcher. Given that the final number of participants in UKISS was less than half the number intended in the study protocol, it is perhaps sur-

prising that there was found to be a significant difference in developmental outcomes in those infants with no identified underlying aetiology, the group that *a priori* was thought to be most likely to show any effect of treatment upon neurodevelopment. However, the fact that the sensitivity analysis including only two further observations that were not reliably classified into aetiological groups removed the statistical significance of this finding illustrates that the finding is borderline rather than robust and might have been due to chance. However, the size of the difference in Vineland ABC score is potentially clinically important, and the 95% confidence interval for this difference ranged from a minimal difference to one that was slightly greater than one population standard deviation.

In UKISS, we hypothesized that any difference in neurodevelopmental outcome would be most readily identified in the subgroup of infants with no identified underlying aetiology for two reasons. First, there was no proven reason for these infants' development to be affected by any underlying neurological disorder. And second, because it would be more likely that this group would have had a normal potential for development prior to the onset of the spasms.

If cessation of spasms at day 14 and better neurodevelopmental outcome are causally related, then hormonal treatments may be the better first treatment, despite their higher relapse rate and despite the fact that, in this study, overall hormonal treatments were not associated with better neurodevelopmental outcome. This hypothesised relationship between early cessation of spasms and better neurodevelopmental outcomes provide justification for measuring later neurodevelopment and analysing the findings by intention to treat analyses, despite potential bias that might occur do to exposure to other medications in those who do not have initial *cessation of spasms* or who later relapse. Any bias introduced by such later exposures is likely to act as a dilutional bias that reduces the magnitude of any true effect. It is likely that there are other

underlying biasing or confounding factors relating to case-mix, such as duration of spasms before treatment and underlying aetiology.

A Cochrane review of studies has found equivocal evidence suggesting that the administration of steroids to neonates might have a deleterious effect upon later neurodevelopment [224]. In this respect, it is reassuring that UKISS showed no evidence of poorer neurodevelopmental outcomes in infants receiving hormonal treatments.

Fourteen months is an early age at which to assess neurodevelopment and may not reliably reflect cognitive function later in life. Any differences might become more marked as further development takes place. However, as infants get older, social and environmental factors that are not so important at 14 months, such as parental educational level, increasingly influence development, and we did not stratify our groups to account for this. In addition, parents and professionals do not want to wait too long before knowing if there is evidence to suggest that early control of spasms might influence development. Because of our findings relating to development at 14 months of age, it is important to know whether any difference between treatment groups persists. UKISS has since been extended with further neurodevelopmental assessments being made at the age of school entry on children whose parents consent to further assessment. This is technically a separate study and has required *de novo* consent from the parents.

6.2.5 Effects of delayed treatment upon neurodevelopmental outcome

Kivity *et al* reported findings from a non-randomised group of children with cryptogenic infantile spasms and assessed their cognitive outcomes using a Hebrew revised version of the Wechsler Intelligence Scale for Children (WISC-

R) [225]. There was a standardised treatment regimen of tetracosactide depot in reducing doses over 10 to 12 weeks (1 mg IM alternate days for 2 weeks, then every 3 days for 2 weeks, then weekly for 4 to 6 weeks, then 0.5 mg weekly for 2 weeks) followed by a second stage of oral prednisone (10 mg daily for 1 month, then 10 mg alternate days for 2 months, then 5 mg alternate days for 2 months, then 2.5 mg alternate days for 1 month or until aged 12 months, whichever is later). This is a larger tetracosactide dose and substantially longer treatment regimen than that of the UKISS study protocol.

They described normal cognition in all 22 infants who received treatment within one month of apparent onset of spasms but in only 6/15 infants who were not treated before the spasms had been present for over one month. Poor cognitive function at the time treatment started was also reported to be a predictor of subsequent poor cognitive function.

Eisermann *et al* reported a retrospective study of 18 children with infantile spasms and Down syndrome, with a statistically significant correlation between lead-time to treatment (which they referred to as "treatment lag") and several outcomes: time to cessation of spasms (Pearson $r = 0.55$, $P = 0.02$); developmental quotient ($r = -0.75$, $P = 0.003$); and a score of autistic features (AF) ($r = 0.57$, $P = 0.04$) [226]. They also reported a correlation between later response to treatment and lower developmental quotient ($r = 0.86$, $P = 0.001$) and with the higher score of autistic features ($r = 0.5$, $P = 0.06$). The strongest correlation was between longer duration of spasms and lower developmental quotient ($r = -0.93$, $P < 0.0001$).

Using a one-month reported duration of spasms prior to treatment intervention as a threshold do define a dichotomous variable, *lead-time to treatment*, data from UKISS did not show a significant relationship between shorter *lead-time to treatment* and better neurodevelopmental outcome, either in an overall analysis or in an analysis stratified by presence or absence of an underlying

aetiology 4.3.2. However, the direction of the differences in mean scores in these groups was the same as that in the studies of Eisermann *et al* and Kivity *et al*, and there is a strong biological plausibility to the argument that longer duration of spasms before effective treatment intervention is associated with poorer neurodevelopmental outcomes.

6.2.6 Value of pre-randomisation stratification variables

The pre-randomisation stratification variables are described in section 5 of the UKISS study protocol (appendix B.1, page 246). The sex and age category variables are explicit and relatively simple. The third pre-randomisation stratification variable is a composite of factors that were thought to be likely to be associated with poorer prognosis for developmental outcomes. This third variable was coded *yes* if there was any one or more of: several current diagnoses (syndromic, chromosomal, or cerebral palsy); a previous diagnosis (neonatal encephalopathy with seizures); or a diagnosis of developmental delay made before onset of spasms. In the context of discussions in West Delphi about the potential unreliability in assessing the time of onset of spasms, the last factor in this composite third variable might be misclassified in a high proportion of cases.

6.2.7 Administrative delays

There were substantial delays in the administration of the study relating to the need to obtain ethical approval from LRECs in addition to the approval given by the MREC; by the need for management approval; and by the reviews and changes to licensed indications for the trial treatments that occurred during the conduct of the study. It might be regarded as bad luck that one of the trial treatments, vigabatrin, underwent a substantial review of safety after the re-

ports of its association with peripheral visual field defects, and such a major review might be anticipated not to occur during future studies. However, this series of events serves to emphasise the importance of systematically comparing new drugs, no matter how popular and apparently effective they appear to be, against more established drugs. I believe that, during the time that UKISS was recruiting centres and enrolling participants, the recognition of potentially serious adverse effects associated with vigabatrin served to shift a balance of preference among many clinicians back to a position of equipoise of preference between hormonal treatments and vigabatrin. However, there remained strong opinions on that matter, as is evident from correspondence appearing in the BMJ from an advisory group that had reassessed the indications for use of vigabatrin [227, 228] and the UKISS trial steering committee [188, 229]. There is no evidence that such administrative tasks have become easier since the time UKISS started to enrol participants, and indeed the procedure for obtaining ethical approval in member countries of the European Union has become standardised in a fashion that many investigators, including members of the UKISS trial steering committee, regard as more onerous than before.

6.2.8 Discussion of response times of local research ethics committees

The methods for obtaining informed consent for clinical trials, and particularly for obtaining consent from parents or guardians of children participating in clinical trials, was a contentious issue at the time this study was conducted. It was becoming accepted that a single signed document is not adequate proof that consent has been obtained and maintained, and that clinical investigators ought to provide some method for ensuring that information is given to carers and permission to continue the research is granted continually. Since no for-

mal method for ensuring continual consent had been developed, the United Kingdom Infantile Spasm Study provided regular newsletters for carers.

The two-tier system of ethical approval by MRECs and LRECs has left room for interpretation of their roles. Our experience was that the MREC and LRECs disagreed in several cases about whether the LREC was entitled to request changes to patient information sheets with respect to an issue that was not peculiarly local. In several cases, these different interpretations led to an impasse in which the MREC did not recommend an amendment suggested by an LREC, and the LREC refused to approve the study without the amendment being made [204]. There are obvious inefficiencies associated with a system of dual ethical approval, but there will always be a need for local input into ethical decisions. Alberti wrote a BMJ editorial that accompanied the publication of the UKISS paper on times taken for ethical approval, revisiting questions he had asked in an editorial preceding the introduction of MRECs [230, 231]. Asking whether cure had been worse than the disease, he concluded that the two-tier system is better but that the main problems resided at the interface between MRECs and LRECs, and that simple methods, such as the standardisation of application forms, would be effective in removing many of the definite obstructions to research.

6.2.9 Adverse events

Randomised controlled trials of treatment are not the best way to collect data about rare but serious adverse events because the numbers enrolled are relatively small. The five deaths reported before the age of 12 months are consistent with the natural history of infantile spasms. One death (study death 1 described on page 163) was considered to have been in part attributable to treatment with prednisolone, but he had been allocated vigabatrin at the time of enrolment and had not responded with *cessation of spasms*. The certified

cause of death was *Staphylococcus aureus* septicaemia, and it was considered that the recognition of clinical signs of septicaemia was delayed as a result of the corticosteroid treatment.

The findings of higher reported rates of irritability with hormonal treatments and drowsiness with vigabatrin are not surprising, since these are recognised adverse effects associated with these treatments. The *P*-values cited in section 3.5.2 are not adjusted for multiple testing, but informally they provide evidence that there are differences in the frequency of these adverse effects between treatment groups. Other adverse events were less common and, because of the study size, statistically significant differences would not be expected even where true differences exist.

6.2.10 Potential roles of chance and bias in UKISS

As with any study, it is possible that the differences detected – both in *cessation of spasms* at study day 14 and in neurodevelopment in the subgroup with no identified underlying aetiology – were due to chance. However, in UKISS the proportion of infants allocated vigabatrin that had *cessation of spasms* was higher than that reported in the randomised studies of Appleton *et al* and Elterman *et al*, making it unlikely that the vigabatrin effect estimate was lower than the true effect by chance. This is in the context of the UKISS randomised trial excluding cases with known or likely tuberous sclerosis, a condition that is generally considered to respond better to vigabatrin than other symptomatic cases of infantile spasms. If there were significant bias introduced by this exclusion criterion, one would have expected the effect estimate for treatment with vigabatrin to have been lower, rather than higher, in UKISS than in these other two studies.

The proportions with cessation of spasms in hormonal treatment and vigabatrin groups were similar in UKISS to those reported by Vigevano and

Cilio, which is the only other published randomised controlled trial comparing adrenocorticotropic hormones with vigabatrin. This repeatability suggests that the estimate of differences in effect is unlikely to have occurred by chance.

The potential absence of any role of chance and bias is less certain with the other main finding: that neurodevelopmental outcome is better in infants allocated hormonal treatment than vigabatrin in the subgroup with no identified underlying aetiology. Most notably, the significance of the difference was not sufficiently robust to withstand a sensitivity analysis that included only two observations that did not have reliable aetiological classifications. As described on page 147, one of these observations was an infant allocated vigabatrin that had a Vineland ABC score of 93 and thus increased the average score for vigabatrin in this group. The other case was allocated tetracosactide and had a a Vineland ABC score of 57, decreasing the score for hormonal treatments. Neither of these cases had had neuroimaging studies. The case allocated vigabatrin was considered by his parents to be too well to merit neuroimaging, which would involve exposure to ionising radiation (for CT scan) or, at his age, would probably require a general anaesthetic (for MRI scan). It is likely that he was a genuine idiopathic/cryptogenic case and that no underlying aetiology would have been found if neuroimaging had been performed. The case allocated tetracosactide died before any diagnosis was made and the parents did not give consent for a post-mortem pathological or radiological examination. It is likely that this case would have had an identifiable underlying cause if such investigations had been performed, and it could be argued that the sensitivity analysis was in this respect unfair to hormonal treatments. However, creating the most extreme case against the effect found is the purpose of sensitivity analyses, and the effect found was at the margin of significance at the 5% level. The appropriate interpretation is that this finding is of scientific interest and invites further investigation, but is itself non-robust.

The direction of the difference in neurodevelopment is different in the other subgroup of infants with an identified underlying aetiology, and there is no ready explanation for this. It is possible that infants with symptomatic aetiologies are more likely to progress to other seizure types and that treatment with an antiepileptic drug, such as vigabatrin, throughout this critical period is associated with better neurodevelopmental outcome because of an effect upon clinical or subclinical seizure control. However, this is speculative and the difference is not statistically significant. Approximately half of infants allocated hormonal treatments received vigabatrin before the end of the study, and *vice versa*. This means that there would be dilution of any true difference in treatment effect because of the differential exposures to treatment.

The finding that *cessation of spasms* was significantly associated with better neurodevelopmental outcome independently of randomised treatment is difficult to interpret. Any effect of randomised treatment would presumably be mediated by earlier cessation of spasms, or at least this would be the most likely mode of mediation. The finding cannot be interpreted as suggesting a chance selection bias in favour of the hormonal treatment since they are not independently predictors of better neurodevelopmental outcome in the overall study sample. The opinion of the UKISS steering committee is that these findings are not robust and merit replication or further testing in future studies; and later study of the current trial cohort is being undertaken to examine whether the apparent effects upon neurodevelopment are sustained. The relatively small sample size precludes valid use of logistic regression methods to adjust more fully for the effects of potential prognostic factors upon the *cessation of spasms* outcome.

6.2.11 Validity and generalisability of findings from UKISS

UKISS used an effectiveness study paradigm, as discussed in section 2.1.3. In this respect, generalisability to cases of infantile spasms diagnosed clinically in the United Kingdom is probably good, although there might be substantial differences in case definitions and required EEG features in specific centres. However, generalisability cannot be made to the group of infants whose underlying aetiology was tuberous sclerosis, since these were excluded from the randomised controlled trial. It is interesting that, although vigabatrin is generally considered to be particularly effective in the treatment of infantile spasms when the underlying aetiology is tuberous sclerosis, the treatment effect obtained in UKISS was better than that in other randomised studies that included cases with tuberous sclerosis [95, 222].

6.2.12 Methodological and procedural insights from UKISS

There were substantial delays in the administration of the study that related to ethical approval and reappraisal in the light of new safety findings, and the administration of trust management approval for the study. Also, accrual of study participants was slower than predicted. It is possible that some cases were not reported because local investigators forgot, during the course of a relatively long study, to notify them. We were aware of several cases where the local investigators' colleagues were not immediately aware or mindful of the study when new cases presented, leading to later notification. However, the greatest procedural insight from UKISS was the realisation that there is substantial heterogeneity in case definitions and outcome measures between studies of infantile spasms, an insight that led to the development of the West Delphi consensus statement.

The study would have been methodologically sounder if neurodevelop-

mental assessments had been made by an assessor who was more effectively blinded to the treatment intervention, but this could not be incorporated reliably into the study design. In practice, it is unlikely that this interfered significantly with the assessment because sufficient time had passed between allocating treatment and performing the assessment that the assessor's knowledge of the trial treatment in any particular case was poor. Further assessment of the reliability of these findings will be possible with later neurodevelopmental assessments.

UKISS excluded cases with proven or likely tuberous sclerosis from the randomised controlled trial. The rationale for this exclusion is discussed in section 2.3.2. It was intended that cases with tuberous sclerosis would be enrolled in the non-randomised element of the study, but accrual of such cases was slow. The preamble to the UKISS study protocol, under the heading *Epidemiology*, clearly states that some patients excluded from the drug trial would be eligible for the non-randomised element of the study, but this did not make specific reference to tuberous sclerosis. The exclusion of tuberous sclerosis cases takes a prominent position in the UKISS study protocol, occurring at the head of section 2 (see page 245). These factors probably combined to lead some local investigators to think that cases with tuberous sclerosis did not need to be notified to the UKISS trial centre.

There is no evidence that exclusion of cases with tuberous sclerosis led to significant bias in findings, as is discussed in section 6.2.10. However, it is interesting to note from analysis of the data on non-randomised cases that, even though vigabatrin was prescribed more frequently than hormonal treatments overall in non-randomised cases, 4/15 infants with tuberous sclerosis were given treatments other than vigabatrin by their local investigator (section 3.3.4 on page 119). This would suggest that, once the study was under way and new information about vigabatrin-associated visual field losses was available,

there was more equipoise towards hormonal or vigabatrin treatment of tuberous sclerosis than the UKISS trial steering committee had anticipated when the study protocol was being designed.

6.2.13 Impact of findings of UKISS

UKISS cannot claim to have definitively answered the question, "Which is the best first-line treatment for infantile spasms?" It is possible that aetiological subgroups will respond better to one or other of the established first-line treatments, or possibly to other less established treatments.

There may be fears that finding vigabatrin to be less effective than ACTH or prednisolone would further compromise its position as a viable drug, perhaps leading to it being withdrawn from production or requiring special status as an *orphan drug*. Certainly, UKISS provides evidence that vigabatrin is not, overall, superior to hormonal treatments, but in isolation it does not definitively prove hormonal treatments to be superior; and it does not fully address the issues of differential effects in specific aetiological subgroups or the role of vigabatrin as rescue treatment in those who fail to respond to hormonal treatments. These are issues that are being considered by the UKISS steering committee for further investigation in new studies.

6.3 Discussion of West Delphi

Reaching consensus on case definitions is not easy. After the WHO and ILAE decided to develop an international classification of epilepsies to accompany the International Classification of Epileptic Seizures, Merlis reported the experiences of the 15 contributors from 12 countries [232].

> The initial period could be described as chaotic, with many divergent approaches being presented and with frequent interruptions of speakers by,

> sometimes, rather warm disagreement ... I think I can say that, despite being hoarse and tired at the end of the day, many, if not all, of the participants felt that it had been an instructive, productive and exhilarating experience.

The rationale behind West Delphi was to propose standard case definitions, outcomes, and outcome measures that would ease future study design; that would facilitate comparison of data from different studies; and that would encourage the design of studies answering questions that are important to clinicians and families seeking reliable and valid information about treatment choices. These aims are essential stages on the road to determining the best treatments for children with infantile spasms, and the West Delphi process dissected many of the issues surrounding case definitions and outcomes. Though there were substantial areas of consensus, there were also several areas of incomplete disagreement.

A Delphi process seemed to be a good way to elicit a consensus of opinion in this setting. Although it is generally considered a way to elicit "expert" opinion, West Delphi aimed to recruit a variety of motivated contributors, not all of whom would necessarily be considered to be experts or from backgrounds in clinical research. Rather, the aim was to have a balance of contributors, some of whom would have a proven record of published research in this area, but others of whom would represent clinicians who would be perhaps more likely to be interpreting and evaluating research than contributing to original research. However, there was also the implicit and secondary long-term aim of encouraging greater participation in future research projects. Although we did not formally classify the contributors to West Delphi as primarily clinical researchers or service-orientated clinicians, I feel there was a balance of contributors that met the above aims, and I hope that many of these will be encouraged to contribute to future clinical research in the area of infan-

tile spasms.

The anonymity associated with the consensus process has substantial advantages and helps to reduce the effects that might limit the contribution of frank and considered opinion. Such factors include fear of embarrassment at presenting views in public; fear of contradicting the views of established opinion leaders in a particular field; fear of presenting novel ideas that might have substantial flaws; fear of being domineered by others; and fear of losing face when changing an opinion. However, there are also potential disadvantages associated with delphi processes. For example, with specific technical issues there might be a lack of insight within the group as a whole and the majority view might have technical flaws. There is the sense in West Delphi that the failure to progress further in EEG definitions was in part due to the group's lack of confidence that its members had insufficient technical skill to address specific technical issues of EEG description and interpretation.

6.3.1 West Delphi proposed case definitions

The West Delphi consensus statement is reproduced in appendix D (page 274). The process aimed, among other things, to propose definitions that are congruent with previous usage and recent ILAE proposals. The proposed 5-axis diagnostic scheme for people with epileptic seizures and with epilepsy was felt to be potentially useful though several changes were suggested as modifications to the scheme [233]. Roger and Dulac used the terms *infantile spasms* and *West syndrome* to refer to syndrome diagnoses, and they suggested the term *epileptic spasms* to refer to a seizure type [25]. The West Delphi consensus evolved to have strong congruence with these definitions. However, there were also examples where it was thought to be be valid and useful to make clear distinctions and departures from previous practice. For example, the contributors found it valuable to use the term *epileptic spasms* to describe the seizure type,

rather than as a phenomenological description as proposed in the ILAE Glossary of Descriptive Terminology, 2001 [234]. And where the ILAE Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy suggests the term *spasms* to describe the seizure type, the West Delphi Group proposed making a distinction between the terms *clinical spasms* to describe seizure phenomenology and *epileptic spasms* to describe the seizure type. The West Delphi Group considered these terms to have strong intuitive appeal.

There was initial disagreement about the status of developmental delay as a defining feature of West syndrome. The consensus was that it is often difficult to determine when spasms started and whether development was normal at that time. Because these are unreliably determined and misclassification is likely, it was agreed that developmental delay at onset of spasms ought not to be a defining feature of infantile spasms.

Much debate focussed on the status of *infantile spasms* as a syndrome and the status of *infantile spasms single-spasm variant* with associated hypsarrhythmia. Some contributors considered there to be an argument for classifying these as seizure types, corresponding to Axis 2 of the proposed ILAE diagnostic scheme. However, overall the West Delphi Group did not find this argument compelling and thought that it is more appropriate to classify *IS* and *ISSV* with hypsarrhythmia as epilepsy syndromes. Within the final consensus statement, the features that define *West syndrome* as a syndrome subgroup of *infantile spasms* are clustering of spasms and hypsarrhythmia.

Defining EEG features was evidently challenging, and several contributors found it difficult to distinguish necessary and sufficient features. In response to round 2, for example, the most popular feature suggested as sufficient was high voltage slow waves, but since slow waves are a non-specific feature of many encephalopathic processes, this is clearly not a sufficient feature of hypsarrhythmia. Some participants suggested that high-voltage slow waves as-

sociated with sharp waves or epileptiform spikes would be sufficient to define hypsarrhythmia, but these are clearly found in combination with other epilepsy conditions and are not sufficient [64]. The West Delphi Group agreed upon a description of hypsarrhythmia rather than a strict definition of limits, and it was agreed that there remains a strong element of *Gestalt* in recognizing this EEG pattern. There have been no studies of intra-rater and inter-rater agreement of classification of EEGs with hypsarrhythmia and its modifying features.

The consensus statement endorsed the proposal made by the 1991 ILAE Workshop that modifying features should be listed separately rather than being regarded in the aggregate as forming a distinct group of EEG types [28]. A list of individual modifying features was given in appendix A of the consensus statement [209] and is reproduced on page 286 in appendix D of this thesis. Since modified EEGs may bear more or less resemblance to *typical* or *classical* hypsarrhythmia, it was felt to be irrational to dichotomise cases on the basis of presence of any one or more modifying features. Such modifying features might relate to a missed temporal window of opportunity for catching a more *typical* recording, since features such as increased synchrony and organisation in the EEG are related to brain development and sleep-wake behavioural state. Or they might relate to underlying causes or triggers of the spasms: for example, increased focality where the trigger is a cortical malformation or tuber.

The consensus was that cases of infantile spasms might occur without hypsarrhythmia, although some participants expressed reservations about this. It is well recognized that hypsarrhythmia is not found throughout the course of infantile spasms. It was noted that some studies, and notably the study of Chiron *et al*, have reported hypsarrhythmia in fewer than half of cases classified as having infantile spasms at the time of randomized treatment [16].

With respect to ISSV without hypsarrhythmia, it was thought to be irra-

tional to exclude these solely by definition if it were acceptable to admit cases with single spasms with hypsarrhythmia and cases with clustered spasms without hypsarrhythmia. However, some contributors were certain that they would never diagnose infantile spasms in such cases, and the consensus was that inclusion of such cases should be explicitly justified with reasons for considering them valid cases of infantile spasms, since spasms that are never observed to cluster and that are not associated with hypsarrhythmia are likely to due to a cause other than infantile spasms. A related issue was that of how long a period might elapse between spasms before they are considered not to be part of the same cluster. A pragmatic opinion was that spasms occurring with a frequency of less than one per minute should be considered to be non-clustered, but there is again no biological plausibility in an absolute and rigid definition based upon elapsed time, and spasms occurring with a periodicity of less than one-per-minute might well be considered to be part of a cluster. This is another example of a case where a pragmatic and somewhat arbitrary definition might be necessary in order to facilitate the collection of standardised and reliable data.

Some contributors thought that unequivocally normal development at the time of onset of spasms was a good prognostic feature, and the consensus evolved to recommend that this should be recorded and used for prognostic factor analysis in studies of infantile spasms. It was suggested that this reframing from apparently delayed development to unequivocally normal development would be useful when counselling families about prognosis.

It was evident from the process of eliciting a consensus that clinicians and investigators have used the terms *infantile spasms* and *West syndrome* variably, and that there has been also great variation in the interpretation of the terms *cryptogenic*, *idiopathic*, and *symptomatic*. Previous ILAE commissions have used the terms idiopathic and cryptogenic as antonyms of symptomatic [34, 35].

Contributors debated these terms a great deal. The eventual consensus was that information about prognosis and treatment response related to specific underlying diagnoses is probably more useful than classification into etiologic subgroups that are themselves heterogeneous.

Consideration was given to potential information bias due to reclassification of cases between enrolment in a study and the time of study completion. It was felt important to clearly distinguish between an etiologic classification made at the time of study enrolment and a diagnostic classification made at the time of study completion. This allows those using information from studies to be clearer about what type of diagnostic information tends to be available at the time of treatment decision; and will also allow investigators to assess the value of specific investigations, such as MRI or CT scans, prior to initiation of treatment.

Some contributors wished to emphasise the limited value of aggregating cases into etiologic subgroups, preferring to look instead at outcomes in groups of children with the same specific underlying disorder. For example, tuberous sclerosis seems to have a better response to treatment with vigabatrin than other cases of symptomatic infantile spasms.

One area of strong controversy was subtle seizures associated with hypsarrhythmia but without evidence of spasms. The consensus was that, while eye or subtle distal limb movements may be regarded as evidence of continual seizure activity, they do not provide a reliable outcome for the purposes of clinical studies since they are likely to be missed without careful observation and are otherwise difficult to count. Even ictal events with more the more typical semiology of spasms have marked variation when ictal events are examined with EEG-video and EMG, but it is possible that such investigations will lead to recognisable and reliable patterns [235].

6.3.2 West Delphi proposed outcome measures

The latter part of the consensus statement (sections 26 onwards) addresses the issue of standardised outcomes and outcome measures for studies of infantile spasms. Few published studies have provided information about even essential outcomes, such as how they defined clinical or electroclinical response. In the early rounds of West Delphi it was evident that most clinicians would not regard cases relapsing within a few weeks as primary clinical responders. However, they agreed that spasms recurring after 28 days of absence are described reasonably as relapse rather than failed primary response. This led to the definition of a primary clinical response, *cessation of spasms*, that is markedly more stringent in its requirement for duration of response than those of previous studies. For example, in UKISS, a case could potentially relapse after little more than 48 hours of freedom from spasms; and the studies of Appleton *et al* and Elterman *et al* respectively required 1 day and 7 days of spasm freedom [95, 222].

In West Delphi, there was a consensus that a treatment has had sufficient opportunity to prove its effect by 14 days, and that it is necessary to give a treatment for this duration before concluding that it has failed to show any treatment effect. It was appreciated that this limit is arbitrary and that there might be good reasons for a new study to use a different duration of treatment. However, it was felt to be useful to suggest a standard, and the consensus suggested that, should investigators choose a different period, they ought to explain their reasons for that choice.

The consensus discussion emphasised the danger of adding an extra degree of subjectivity to study design and impeding aggregation of data by permitting study designs that might, for example, favour a drug that is reputed to act more quickly than another. Such factors would be better investigated by other

means than altering the primary outcome, such as modelling time to cessation of spasms. Such an approach would preserve a reasonable degree of study standardisation and would facilitate comparison and aggregation of data from studies and, in the longer term, would provide better information for clinicians and families.

The consensus proposed three categories of age at onset of spasms (or more correctly, age at apparent onset of spasms, since timing can be unreliable) not with the aim of creating further subgroups for stratified randomisation, but rather to identify age at onset as a potential prognostic factor that should be considered in the analysis of trial data.

There was a good deal of negotiation about the most appropriate primary outcome. Most participants were keen on emphasising the clinical response, but others were sceptical at the idea of suggesting a response had occurred when the EEG still showed hypsarrhythmia. There are issues relating to the timing of EEG samples. Observation for seizures such as clinical spasms is a more-or-less continuous process, although this lacks sensitivity if one is interested in more subtle spasms or focal seizures. In contrast, EEGs performed at set times according to a study protocol are cross-sectional observations and, because of this form of sampling in time, are also insensitive. The final consensus was that there should be reporting of two proper primary outcomes: the primary clinical outcome and the primary electroclinical outcome as defined above. The finally approved approach of reporting both outcomes has many advantages, and the analysis of data from future studies reporting both outcomes should provide further information about their usefulness.

6.3.3 Methodological and procedural problems with West Delphi

There were several procedural problems with West Delphi. Many rounds had to be extended to permit late responses to be sent, and not all contributors participated in all rounds (table 5.1, page 170). However, the final statement was agreed by all contributors. Also, there were occasionally responses that revisited questions that had been addressed in previous rounds. The last two rounds consisted to a large degree on discussion of the paper for publication, though specific issues of consensus were still being debated.

A strict interpretation of the guidelines for a Delphi process would not have permitted conferring by West Delphi contributors who were also members of the Königsteiner Kreis, a group of German and Swiss doctors with an interest in pediatric epilepsy that deferred completion of an ongoing consensus statement while several of its members contributed to West Delphi. The fact that the opinions of those members formed a single response rather than several responses for West Delphi prevented any significant bias being introduced from coordinated responses. However, it may have had the converse effect of reducing the influence of their opinions where those opinions were in agreement before any consultation took place.

6.3.4 Summary of West Delphi

The West Delphi Group consisted of 31 clinicians and investigators, including the author (who acted as facilitator), who have an interest in infantile spasms. The process involved novel suggestions and lively debate. Relatively few cases of infantile spasms are enrolled into formal studies. To reliably and convincingly evaluate treatments, and to investigate potential variation in responses in different diagnostic groups, we should consider more collaborative and in-

ternational studies, and to aggregate data from disparate studies. West Delphi is a useful contribution to this process. The issue of underlying aetiology and its classification is likely to evolve and to remain controversial, and it is likely that future consensus statements will have to revisit this issue. The area that was least satisfactorily addressed was defining clearer limits on the classification of EEG features, and this too will need to be addressed in the development of future consensus statements.

Although there is to date no published appraisal of the West Delphi Group's consensus statement and it has not attracted any published correspondence, informal feedback from sources has suggested that it is regarded as a sound basis for study design in this area and that studies designed according to its proposals are likely to gain wide acceptance. Along with the publication of UKISS, it is leading to renewed interest in larger studies of infantile spasms.

6.4 Considerations for future studies

The United Kingdom Infantile Spasms Study showed a clinically important difference in *cessation of spasms* at study day 14 and an association between this outcome variable and later neurodevelopmental scores in infants with no identified underlying cause for their infantile spasms. However, UKISS did not provide compelling evidence of a clear causal pathway that was free from bias and confounding, and that led directly from treatment intervention to cessation of spasms, and thence to better neurodevelopment. The UKISS findings have prompted further questions, and an International Collaborative Infantile Spasms Study has been designed to investigate this further. The steering group for the international study includes members of the UKISS steering committee. This study will investigate, among other things, whether combined vigabatrin and hormonal treatment will result in better early spasm control and better

neurodevelopment.

There remains a paucity of reliable population-based information on the incidence of infantile spasms and the relative prevalence of specific underlying aetiologies. Providing such information was one of the motivations behind UKISS, but many factors conspired to make a reliable epidemiological study impossible. These factors included the volume of work associated with administering the randomised controlled trial, under-reporting of non-randomised cases, and delays associated with ethical and management approval that substantially staggered the times at which recruiting centres came on-line.

One way to improve notification and accrual of cases for a reliable population-based epidemiological study would be to ensure that there is clear nesting of cases allocated random treatments within a larger group that are enrolled to provide epidemiological information. This might be possible in collaboration with established surveillance systems, such as the British Paediatric Surveillance Unit. Potential underlying causes might be classified using the system suggested in the West Delphi consensus statement, and a study protocol might suggest an algorithmic approach to appropriate investigations to standardise such aetiological classification.

6.5 Conclusions of this thesis

The United Kingdom Infantile Spasms Study was large by comparison with most previous studies, and is the largest comparative head-to-head study of different treatments to date. It investigated the most popular treatments currently used in the United Kingdom and Europe and found that cessation of spasms in response to treatment, measured by using a variable that related to absence of observed spasms on days 13 and 14 after randomised treatment, was commoner in infants who were allocated hormonal treatments. However,

relapse was less common in infants treated with vigabatrin, and overall the proportions with relapse-free cessation of spasms was similar in the groups allocated hormonal treatment and vigabatrin. There were no significant differences in neurodevelopmental outcome at the age of 14 months, but there was a non-robust finding that infants with no identified underlying aetiology had better scores if allocated hormonal treatments rather than vigabatrin.

Further investigation of issues identified in the process of conducting this study are already being addressed by the UKISS steering committee. Later developmental assessments are likely to be more discriminatory than assessments performed at the age of 14 months, and these assessments are now being conducted. And there is the question of whether a combination of hormonal treatment and vigabatrin will be associated with better neurodevelopment than hormonal treatments alone.

The conduct of the study highlighted several important aspects, such as the delays introduced by the need for ethical approval and management approval on many sites. However, it highlighted above all the lack of definition that has accompanied many previous studies. The pursuit of better definition and greater standardisation of outcome measures led to the development of the West Delphi consensus statement. Informal and unpublished reaction to this published statement suggest that it will be regarded as a reliable and valuable guide to study design in the area of infantile spasms for many years.

Appendix A

Study contributors

A.1 Members of the UKISS Trial Steering Committee

John P. Osborne, Professor of Paediatrics and Child Health,
School for Health, University of Bath; and
Consultant Paediatrician, Department of Child Health,
Royal United Hospital, Bath, UK.
(Chair of Steering Committee)

Stuart W. Edwards, Research Fellow,
Bath Unit for Research in Paediatrics,
Royal United Hospital, Bath, UK.
(Study Administrator)

Eleanor Hancock, Clinical Research Fellow,
Bath Unit for Research in Paediatrics,
Royal United Hospital, Bath, UK.

Anthony L. Johnson, Statistician,
Medical Research Council Biostatistics Unit,
School of Public Health, University of Cambridge, Cambridge, UK.
(Study Statistician)

Colin R. Kennedy, Consultant Paediatric Neurologist,
Department of Paediatrics,
Southampton General Hospital, Southampton, UK.

Andrew L. Lux, Clinical Research Fellow,
Bath Unit for Research in Paediatrics,
Royal United Hospital, Bath; and
Specialist Registrar in Paediatric Neurology,
Bristol Royal Hospital for Children and Frenchay Hospital, Bristol, UK.
(Author of this thesis)

Richard W. Newton, Consultant Paediatric Neurologist,
Department of Paediatric Neurology,
Royal Manchester Children's Hospital, Manchester, UK.

Finbar J.K. O'Callaghan, Clinical Research Fellow,
Bath Unit for Research in Paediatrics,
Royal United Hospital, Bath; and
Consultant Paediatric Neurologist,
Bristol Royal Hospital for Children and Frenchay Hospital, Bristol, UK.

Christopher M. Verity, Consultant Paediatric Neurologist,
Department of Paediatrics,
Addenbrooke's Hospital, Cambridge, UK.

A.2 Members of the UKISS Data Monitoring and Ethics Committee

Philip J. Milner, Professor of Public Health,
Department of Medical Sciences,
University of Bath, Bath, UK
(Chair of DMEC until April 2002).

Christopher N. Martyn, Clinical Scientist,
Medical Research Council Environmental Epidemiology Unit,
University of Southampton; and
Consultant Neurologist, Wessex Neurological Centre,
Southampton General Hospital, Southampton, UK
(Chair of DMEC from April 2002).

R. Mark Gardiner, Professor of Paediatrics,
Department of Paediatrics and Child Health,
Royal Free and University Hospital Medical School, London, UK.

Christopher Jennison, Professor of Statistics,
Department of Mathematics,
University of Bath, Bath, UK.

Jane Schulte, Consultant Community Paediatrician,
North Bristol NHS Trust,
Westgate House, Southmead Hospital, Bristol, UK.

John Wilson, Retired Consultant Paediatric Neurologist,
Department of Paediatric Neurology,
Great Ormond Street Hospital for Children, London, UK.

A.3 Centres and local investigators approved to enroll cases in UKISS

Addenbrooke's Hospital, Cambridge
Alexandra Hospital, Redditch
Altnagelvin Area Hospital, Londonderry
Antrim Hospital, Antrim
Barnet General Hospital, Barnet
Basildon Hospital, Basildon
Birmingham Children's Hospital, Birmingham
Birmingham Heartlands Hospital, Birmingham
Bishop Auckland General Hospital, Bishop Auckland
Blackpool Victoria Hospital, Blackpool
Booth Hall Children's Hospital, Blackley
Bristol Royal Hospital for Children, Bristol
Central Middlesex Hospital, London
Chase Farm Hospital, Enfield
Cheltenham General Hospital, Cheltenham
Child Development Unit, Watford
Children's Centre, Dorchester
City Hospital, Birmingham
Colchester General Hospital, Colchester
Coleraine Hospital, Coleraine
Conquest Hospital, St Leonards on Sea
Countess of Chester Hospital, Chester
County Hospital, Hereford
Crawley Hospital, Crawley
Cumberland Infirmary, Carlisle
Daisy Hill Hospital, Newry
Darlington Memorial Hospital, Darlington
Derbyshire Children's Hospital, Derby
Derriford Hospital, Plymouth
Diana Princess of Wales Hospital, Grimsby
Doncaster Royal Infirmary, Doncaster
Dryburn Hospital, Durham
Eastbourne District General Hospital, Eastbourne
Epsom General Hospital, Epsom
Fairfield General Hospital, Bury
Farnborough Hospital, Orpington
Frenchay Hospital, Bristol
Furness General Hospital, Barrow-in-Furness

Glan Clywd District General Hospital, Rhyl
Gloucestershire Royal Hospital, Gloucester
Great Ormond Street Hospital & Institute of Child Health, London
Guy's Hospital, London
Harrogate District Hospital, Harrogate
Hartlepool General Hospital, Hartlepool
Havering Hospital, Romford
Hemel Hempstead General Hospital, Hemel Hempstead
Hinchingbrooke Hospital, Huntingdon
Ipswich Hospital, Ipswich
James Paget Hospital, Great Yarmouth
John Radcliffe Hospital, Oxford
Joyce Green Hospital, Dartford
Kettering General Hospital, Kettering
King George Hospital, Goodmayes
King's College Hospital, London
King's Mill Hospital, Sutton-in-Ashfield
Kingston Hospital, Kingston-upon-Thames
Leighton Hospital, Crewe
Lincoln County Hospital, Lincoln
Lister Hospital, Stevenage
Macclesfield District General Hospital, Macclesfield
Mayday University Hospital, Thornton Heath
Medway Maritime Hospital, Gillingham
Mid Ulster Hospital, Magherafelt
Milton Keynes General Hospital, Milton Keynes
New Cross Hospital, Wolverhampton
Newcastle General Hospital, Newcastle-upon-Tyne
Newham General Hospital, London
Norfolk & Norwich Hospital, Norwich
North Devon District Hospital, Barnstaple
North Hampshire Hospital, Basingstoke
North Middlesex University Hospital, London
North Tees General Hospital, Stockton-on-Tees
North Tyneside General Hospital, North Shields
Northwick Park Hospital, Harrow.
Ormskirk & District General Hospital, Ormskirk
Pembury Hospital, Tunbridge Wells
Pilgrim Hospital, Boston
Pontefract General Infirmary, Pontefract
Poole General Hospital, Poole

Royal Preston Hospital, Preston
Princess Margaret Hospital, Swindon
Princess Royal Hospital, Telford
Queen Elizabeth II Hospital, Welwyn Garden City
Queen Elizabeth Hospital, Gateshead
Queen Elizabeth Hospital, Greenwich
Queen Elizabeth Hospital, King's Lynn
Queen Elizabeth the Queen Mother Hospital, Margate
Queen Mary's Hospital for Children, Carshalton
Queen's Medical Centre, Nottingham
Queen's Park Hospital, Blackburn
Raeden Centre, Aberdeen
Royal Aberdeen Children's Hospital, Aberdeen
Royal Albert Edward Infirmary, Wigan
Royal Alexandra Hospital for Sick Children, Brighton
Royal Belfast Hospital for Sick Children, Belfast
Royal Berkshire Hospital, Reading
Royal Bolton Hospital, Bolton
Royal Cornwall Hospital, Truro
Royal Devon & Exeter Hospital, Exeter
Royal Free Hospital, London
Royal Glamorgan Hospital, Llantrisant
Royal Gwent Hospital, Newport
Royal Hampshire County Hospital, Winchester
Royal Lancaster Infirmary, Lancaster
Royal London Hospital, London
Royal Manchester Children's Hospital, Pendlebury
Royal Shrewsbury Hospital, Shrewsbury
Royal Surrey County Hospital, Guildford
Royal United Hospital, Bath
St Albans City Hospital, St Albans
St Ann's Hospital, London
St John's Hospital, Chelmsford
St Mary's Hospital, London
St Mary's Hospital, Newport (Isle of Wight)
St Mary's Hospital, Portsmouth
St Peter's Hospital, Chertsey
Salisbury District Hospital, Salisbury
Sandwell General Hospital, West Bromwich
Singleton Hospital, Swansea
Stafford District General Hospital, Stafford

Stepping Hill Hospital, Stockport
Stoke Mandeville Hospital, Aylesbury
South Cleveland Hospital, Middlesborough
Southend Hospital, Westcliff-on-Sea
Southampton General Hospital, Southampton
Southmead Hospital, Bristol
Southport District General Hospital, Southport
Sunderland Royal Hospital, Sunderland
Tameside General Hospital, Ashton-under-Lyne
Taunton & Somerset Hospital, Taunton
Thelma Golding Centre, London
Thorpe Coombe Hospital, London
Trafford General Hospital, Manchester
Ulster Hospital, Dundonald
University Hospital Lewisham, London
University Hospital of Wales, Cardiff
Walsall Manor Hospital, Walsall
Walsgrave Hospital, Coventry
West Cumberland Hospital, Whitehaven
West Middlesex University Hospital, Isleworth
West Suffolk Hospital, Bury St Edmunds
Weston General Hospital, Weston-Super-Mare
Whiston Hospital, Prescot
Whittington Hospital, London
William Harvey Hospital, Ashford
Wirral Hospital, Wirral
Wordsley Hospital, Stourbridge
Worthing Hospital, Worthing
Wycombe Hospital, High Wycombe
Wythenshawe Hospital, Manchester
Yeovil District Hospital, Yeovil

Dr Simon Ackroyd (Cheltenham)
Dr M AS Ahmed (Goodmayes)
Dr Asya Al-Kharusi (Southport)
Dr Muna Alwaidh (Prescot)
Dr Patricia Atkinson, Dr Abdelhadi Abdelhadi (Crawley)
Dr Thulasi Balakumar, Dr Alison Groves,
Dr Diab Haddad (Chertsey)
Dr Deborah Barff (Weston Super Mare)
Dr Richard Beach (Norwich)
Dr John Beesley (Gateshead)
Dr Angela Bell (Dundonald)
Dr Jeffrey Bissenden (Birmingham)
Dr Marilyn Black (Poole)
Dr Sandy Blewett, Dr Marian McGowan,
Dr David Ogilvie (Carshalton)
Dr Andrew Boon (Reading)
Dr Alan Bosley, Dr Mark Hughes (Barnstaple)
Dr Edward Broadhurst,
Dr Heather Mackinnon (London)
Dr Andrew Butterfill (Hereford)
Dr Duncan Cameron (Rhyl)
Dr Ruth Charlton (Epsom)
Dr Ravi Chinthapalli (Swindon)
Dr Michael Clarke, Dr Keith Lacey (Stockport)
Dr Colin Close, Dr Rowena Sankey,
Dr Shahid Ghazi (Redditch)
Dr Nigel Coad, Dr Maybelle Tatman,
Dr Tariq Ahmad (Coventry)
Dr Gail Collins (Doncaster)
Dr David Cook, Dr Ese Ikhena (Margate)
Dr Christopher Corkey (Newry)
Dr Andrew Cottrell, Dr William Lamb (Bishop Auckland)
Dr Selwyn D'Costa (Dartford)
Dr Peter Dale (Newport)
Dr Menaka De Silva (Orpington)
Dr Penny Dison, Dr Angela Moore (Wolverhampton)
Dr R M Downes, Dr Richard McGucken (Wigan)
Dr Nicholas Driver, Dr Helen Foley,
Dr Charles Godden (Guildford)
Dr Alison Earley, Dr Kamal Sawhney (High Wycombe)
Dr Megan Eaton (Yeovil)
Dr Anthony Edelsten (Great Yarmouth)
Dr Hany El-Naggar (St Albans & Hemel Hempstead)
Dr Andrew Evans, Dr Helen Issler (Greenwich)
Dr Anthony Fan (Grimsby)
Dr Theo Fenton, Dr Helen Underhill (Thornton Heath)
Dr Amanda Freeman, Dr Richard Hallett (Portsmouth)
Dr Jeffrey Freeman,
Dr Albert Massarano (Ashton-U-Lyne)
Dr Frances Gibbon, Dr Sandeep Jayawant (Cardiff)
Dr John Gibbs (Chester)
Dr Jim Gould, Dr Christopher Yale, Dr Kevin O'Neill,
Dr Michael Bamford (Ipswich)
Dr Donncha Hanrahan, Dr Elaine Hicks (Belfast)
Dr Gary Hartnoll (London)
Dr Mohammed Hassoon (Pontefract)
Dr John Heckmatt (Watford)
Dr Frank Hinde (Telford)
Dr Daniel Hindley (Bury)
Dr Wheldon Houlsby (North Shields)
Dr Elaine Hughes, Dr Jean Pierre Lin, Dr Keith Pohl,
Dr Stephanie Robb (London)
Dr Adrian Hughes (Wirral)
Dr John Hyde (Stevenage)
Dr Philip Jardine, Dr Jayesh Patel,
Dr Peta Sharples (Bristol)
Dr Rasieka Jayatunga (West Bromwich)
Dr Mary Johnson (Blackpool)
Dr Robert Jones, Dr Carolyn Adcock,
Dr Tony Cronin (Plymouth)
Dr Eman Jurges (Kingston Upon Thames)
Dr Colin Kennedy, Dr Fenella Kirkham,
Dr Neil Thomas (Southampton)
Dr David Kindley, Prof Josef Egger (Aberdeen)
Dr Pravin Lakhani, Dr Vanda Joss,
Dr Philip Latham (Milton Keynes)
Dr Su Laurent (Barnet)
Dr Geoffrey Lawson, Dr Sam Richmond (Sunderland)
Dr Daniela Lessing, Dr Alex Habel (Isleworth)
Dr Helen Lewis (Manchester)
Prof Sam Lingam (London)
Dr Anthony Lipscomb, Dr Mahesh Babu (Chelmsford)
Dr Maurice Little, Dr Bhavdeep Jani (Gillingham)
Dr Andrew Lloyd Evans (London)
Dr Calum MacLeod (Magherafelt)
Dr Adelaida Martinez (London)
Dr Sateesh Mathew (London)
Dr Anne McGeechan, Dr Jim Barnes,
Dr Robert Scott-Jupp (Salisbury)
Dr Colin Melville, Dr Shomik Ghosal (Stafford)
Dr Richard Miles (Huntingdon)
Dr Andrew Mitchell (Basingstoke)
Dr John Morgan (Llantrisant)
Dr Richard Morton, Dr Keith Dodd (Derby)
Dr Douglas Munro (Harrogate)
Dr Charith Nanayakkara (Kettering)
Prof Brian Neville, Dr Carlos de Sousa (London)
Dr Richard Newton, Dr Omar Ismayl,
Dr Tim Martland (Pendlebury)
Dr Stuart Nicholls (Worthing)
Dr John Nicholson (Antrim)
Dr Catherine Noone (Aylesbury)
Dr Heidi Northover (Bolton)
Dr Sue O'Halloran (Ormskirk)
Dr Corina O'Neill, Dr Gerald McEnery (London)
Dr Anas Olabi (Barrow-in-Furness)
Prof John Osborne (Bath)
Dr John Owens (Macclesfield)
Dr Sunny Philip, Dr William Whitehouse,
Dr Caroline Ross (Birmingham)
Dr Mike Pike, Dr Tony McShane,

Figure A.1: Contributors to UKISS with lead local investigators in bold (part 1) as they appear on *Lancet* website.

Dr Mark Hunter (Oxford)
Dr Sheila Precious (Whitehaven)
Dr Bob Pugh (Crewe)
Dr Richard Purvis (Dorchester)
Dr Rosaline Quinlivan (Shrewsbury)
Dr Murray Quinn (Londonderry)
Dr Michael Quinn, Dr Corinne Hayes, Dr Ronald Smith,
Dr Stella Imong (Exeter)
Dr Karl Rakshi (Blackburn)
Dr Venkat Ramesh (Newcastle upon Tyne)
Dr Chaniyil Ramesh, Dr Monica Placzek (Lancaster)
Dr Martin Robards (Tunbridge Wells)
Dr Stephen Roberts (Manchester)
Dr Claire Rohan (Enfield)
Dr Mark Rollins (Coleraine)
Dr Helen Roper, Dr Roopa Mulik, Dr Andrew Riordan,
Dr Richard Mupanemunda (Birmingham)
Dr Mary Rossiter (London)
Dr Piers Rowlandson (Newport, IOW)
Dr Alastair Scammell,
Dr Christopher Groggins (Lincoln)
Dr David Schapira (Winchester)
Dr Ruby Schwartz (London)
Dr Hilary Scott (Bury St Edmunds)
Dr David Scott (St Leonards on Sea)
Dr B N V Setty, Dr Jane Vaizey (Boston)
Dr Arvind Sharma (Stourbridge)
Dr Alison Shurz (Welwyn Garden City)
Dr Gyanranjan Sinha (Walsall)
Dr Sivaranjini Sriskandan (Westcliff on Sea)
Dr Oliver Stanley (Bristol)
Dr David Stevens (Gloucester)
Dr Hugh Stewart (Durham)
Dr Catriona Stuart (Carlisle)
Dr Geeta Subramanian (Romford)
Dr David Symon,
Dr Puthuvalparampu S Sivakumar (Hartlepool)
Dr John Symons (Colchester)
Dr Andrew Tandy (Taunton)
Dr Graham Taylor, Dr Paul Munyard (Truro)
Dr Indra Thakur (Darlington)
Dr Win Tin, Dr Jonathan Wyllie (Middlesborough)
Dr Pam Tomlin (Preston)
Dr John Trounce, Dr Katherine Anderson (Brighton)
Dr Christopher Verity, Dr Alasdair Parker (Cambridge)
Dr Stephen Ware (Basildon)
Dr Elizabeth Wearmouth (Eastbourne)
Dr Mary Wheater, Dr Dennis Barter (King's Lynn)
Dr Cathy White (Swansea)
Dr William Whitehouse, Dr David Mellor,
Dr Gabriel Chow (Nottingham)
Dr Karen Whiting (Stockton on Tees)
Dr Stuart Williamson (Ashford)
Dr Judith Wilson (Harrow)
Dr Paul Worsley (Sutton-in-Ashfield)

Figure A.2: Contributors to UKISS with lead local investigators in bold (part 2) as they appear on *Lancet* website.

A.4 Members of the West Delphi Group

Andrew L. Lux, University of Bath, Bath, UK (Facilitator and guarantor)
John P. Osborne, University of Bath, Bath, UK (Guarantor)
Giuliano Avanzini, Istituto Neurologico *C. Besta*, Milan, Italy
Tallie Z. Baram, University of California at Irvine, Irvine, CA, USA
Roberto Caraballo, Hospital Nacional de Pediatría, Buenos Aires, Argentina
Kevin Farrell, University of British Columbia, Vancouver, Canada
Tiziana Granata, Istituto Neurologico *C. Besta*, Milan, Italy
Ellie Hancock, Great Ormond Street Hospital, London, UK
Masatoshi Ito, Shiga Medical Center for Children, Moriyama, Japan
Jun Kohyama, Tokyo Medical and Dental University, Tokyo, Japan
Roshan Koul, Sultan Qaboosh Hospital, Alkhad, Oman
Wei-Ling Lee, National Neuroscience Institute, Singapore
Jianxiang Liao, Shenzhen Children's Hospital, Shenzhen, Chin
Marissa B. Lukban, University of the Philippines College of Medicine, Manila
Anthony G. Marson, University of Liverpool, Liverpool, UK
Aida R. Mendoza-Salonga, University of the Philippines College of Medicine, Manila
Brian Neville, Institute of Child Health, London, UK
Harry O. Nomayo, Klinikum Weiden Kinderklinik, Weiden, Germany
Hirokazu Oguni, Tokyo Women's Medical University, Tokyo, Japan
Shunsuke Ohtahara, Okayama University Medical School, Okayama, Japan
Hian-Tat Ong, National University Hospital, Singapore
Desiderio Pozo Lauzan, William Soler Children's Hospital, Havana, Cuba
Dietz Rating, University of Heidelberg, Heidelberg, Germany
Bernhard Schmitt, University Children's Hospital, Zurich, Switzerland
Malinee A. Thambyayah, Hospital Selayang, Kuala Lumpur, Malaysia
Federico Vigevano, Ospedale Pediatrico Bambinu Gesù, Rome, Italy
Anannit Visudtibhan, Mahidol University, Bangkok, Thailand
William Whitehouse, University of Nottingham, Nottingham, UK
Virginia Wong, The University of Hong Kong, Hong Kong SAR, China
Hideo Yamanouchi, Dokkyo University School of Medicine, Tochigi, Japan
Chainllie Young, Washington University School of Medicine, St Louis, MO, USA
Zhongshou Zhou, China-Japan Friendship Hospital, Beijing, China

Appendix B

The UKISS Study Protocol

B.1 Protocol approved by Multicentre Research Ethics Committee

The following text is the Protocol of the United Kingdom Infantile Spasm Study as approved in September 1998 by the South and West Multicentre Research Ethics Committee.

This is a pragmatic drug trial of the current, most common treatments using the clinician's normal investigation plan.

EPIDEMIOLOGY

NOTIFY *ALL* CASES OF INFANTILE SPASMS.

Please notify all cases of infantile spasms to the trial centre even if you do not intend to recruit the individual patient, for whatever reason, into the trial. Any patient with a clinical diagnosis of infantile spasms should be included even if the EEG turns out to be normal. This would include patients younger than 2 months or older than 1 year. It would be very helpful if all cases can be notified so that we know how representative our trial population is compared to the whole UK population. Brief clinical details will be requested.

In order to carry out a capture-recapture analysis of the UK population with IS (thus allowing a more complete ascertainment of cases), we shall ask for information from pharmacists and EEG departments in collaborating hospitals. This information will be initials, date of birth and sex. The clinician will then be approached for pre-randomisation stratification data.

DRUG TRIAL

1. INCLUSION CRITERIA FOR DRUG TRIAL

All infants shall be included of either sex aged at seizure onset between 2 completed

calendar months and 1 year of age (up to but not including their first birthday) who are resident in the UK and who have a clinical diagnosis of infantile spasms from any cause.

2. EXCLUSION CRITERIA FOR DRUG TRIAL

1. Infants who are either known to suffer from tuberous sclerosis (TSC) or who are at high risk i.e. a presumptive diagnosis of tuberous sclerosis because of:
   (a) known affected parent
   (b) previously diagnosed cardiac rhabdomyoma
   (c) hypomelanic macules, a forehead fibrous plaque or shagreen patch noted
   (d) a retinal phakoma seen
   (e) polycystic kidneys in the infant We recommend that first line therapy in these infants should be vigabatrin (see later for dosage). Please inform trial centre even though they will not be entered into the trial.
2. Infants previously treated with vigabatrin or steroids within 28 days of the first diagnosis of infantile spasms.
3. Infants with a contra-indication to vigabatrin or steroids.
4. Infants with a lethal or potentially lethal other condition.
5. Previous treatment for infantile spasms.
6. Inability of parents or guardians to give informed, signed consent.
7. Infants expected to leave the UK within one month of randomisation.
8. Inability of parents or guardians to know when spasms stop - to the nearest whole day.
9. Infants enrolled in a concurrent trial that either uses therapy that might affect the outcome measures of the UKISS trial or one that is time/ effort consuming for the patients/ guardians or the infants' medical practitioners.

All excluded infants should be reported to the trial centre.

3. CONSENT

The trial should then be discussed with the parents or guardians and their consent requested for participation in the trial. Please report any infants where consent is not obtained to the trial centre.

4. ELECTROENCEPHALOGRAM (EEG)

An EEG (or video EEG) should be obtained as quickly as possible so that treatment can start within 72 hours of diagnosis. Only if this is not possible and only if your normal practice is to start treatment prior to an EEG (or video EEG) may you randomise before an EEG (or video EEG) is obtained. If the EEG (or video EEG) is normal, a sleep EEG

will be required prior to randomisation, if this has not already occurred. If the sleep EEG is normal the child will be excluded from the drug trial (unless already enrolled) but please report the exclusion to the trial centre for further follow up. If there will be a delay of more than 72 hours before the EEG (or video EEG) can be performed and it is not your normal practice to start treatment prior to EEG (or video EEG), the child will be excluded from the drug trial (but please report the exclusion to the trial centre for further follow up).

5. PRE-RANDOMISATION

Prior to entry into the study the children will be stratified for randomisation by three variables:

1. By gender: male, female
2. By age: 60 to 119 days; 120 to 179 days; 180 to 239 days; 240 days and over
3. By diagnosis known at time of randomisation (Yes / No).
   (a) a proven chromosomal abnormality
   (b) a proven syndrome diagnosis
   (c) a diagnosis of cerebral palsy made before the onset of the infantile spasms
   (d) a diagnosis of neonatal encephalopathy with seizures
   (e) a diagnosis of delayed development having already been made *before* the onset of the spasms. The diagnosis should have been made by either a medical practitioner or a health visitor, and *must have been made before* the onset of the spasms.

Stratification is being done not to provide definitive groups for subanalysis but to balance the treatment groups with respect to factors which are identifiable at randomisation and which might affect our outcome measures.

6. RANDOMISATION

This will involve central randomisation by telephone call which will register the child into the trial, report base-line information and allocate initial treatment using the method of minimisation balancing over three factors.

7. TREATMENT GROUPS

All children eligible for the trial will then be randomised into two treatment groups: Vigabatrin and "Steroids". All patients randomised to receive "steroids" will undergo a second randomisation, at that time, to either Synacthen Depot or prednisolone. The only pharmacological intervention for the infantile spasms in the first two weeks will be the use of the drug to which each patient has been randomised.

8. INITIAL TREATMENT

This will be a period of two weeks during which the child will receive the drug to which they are allocated as monotherapy. It is the local doctor's responsibility to read the manufacturer's drug data sheet before prescribing the following drugs:

Vigabatrin

Give 50 mg/kg/day orally in two divided doses for 24 hours (i.e. a total of 2 doses). Then increase to 100 mg//kg/day orally in two divided doses in all patients. If at 96 hours seizure control has not been achieved then the dose should be further increased to 150 mg/kg/day orally in two divided doses. They then continue on this dose (100 or 150 mg/kg/day) until the time of their final developmental assessment around 12–14 months of age unless no response or relapse occurs (see below), or this is not your normal practice.

ACTH – USE SYNACTHEN DEPOT

As ACTH gel is not available in the UK, we have substituted Synacthen® Depot. Give 0.5 mg on alternate days (equivalent to 40 iu/day of ACTH) intramuscularly (regardless of age or weight) for two weeks. If at the end of the first week seizure control has not been achieved then the dose should be further increased to 0.75 mg on alternate days (equivalent to 60 iu/day of ACTH) intramuscularly. This group will then tail on oral prednisolone over 15 days. Those on 0.5 mg on alternate days of Synacthen Depot will receive 30 mg of oral prednisolone for 5 days, then 20 mg for 5 days then 10 mg for five days and stop. Those on 0.75 mg on alternate days of Synacthen Depot will receive 40mg of oral prednisolone for 5 days then 20 mg for 5 days then 10 mg for 5 days then stop.

Prednisolone

Give 10 mg q.d.s. orally (regardless of age or weight) for two weeks. If at the end of the first week seizure control has not been achieved the dose should be increased to 20 mg t.d.s. orally. This group will then tail on oral prednisolone over 15 days. Those on 40 mg (10 mg q.d.s.) will reduce to 30 mg for 5 days, then 20 mg for 5 days then 10 mg for five days and stop. Those on 60 mg (20 mg t.d.s.) will reduce to 40 mg for 5 days then 20 mg for 5 days then 10 mg for 5 days then stop.

9. INVESTIGATIONS

(a) An investigation of the child's development will be made by history. At enrolment the clinician will be asked to record the best development ever made on history by the child. It will not be necessary to record the age at which this performance was made. They will then be asked to record the current development achieved.

(b) As part of normal practice in the investigation of infants with infantile spasms, we assume the following investigations will be undertaken:

1. MRI or CT of the brain
2. Urine metabolic screen for amino acids
3. Ophthalmoscopy (either direct or indirect)
4. Ultraviolet light examination (Woods light) The results of these tests should be forwarded to the trial centre. If for any reason one or more of these tests is not completed the reason should be stated.

(c) The following tests may be considered appropriate in some cases and, if performed, the results of these and any other tests should be forwarded to the trial centre.

1. Urea and electrolytes
2. Liver function tests
3. Chromosomes
4. Urine metabolic screen for organic acids
5. Lactate
6. Biotinidase assay
7. Ammonia
8. Thyroid function
9. Pyridoxine response - if pyridoxine is to be given we would recommend that pyridoxine is given one month after the start of the trial (after both the randomised treatment and first alternate treatment have been given in a child who continues fitting).

(d) When venesection is performed for any clinical reason during the course of the infant's illness, please take a blood sample for DNA analysis (bottle, form and addressed sample box included in patient pack). A subgroup of those on steroids will have blood taken to measure cortisol levels.

10. INITIAL OBSERVATIONS

The patient will be admitted if necessary for clinical confirmation for the diagnosis of infantile spasms. If commencing treatment of steroids, the patient will preferably be detained in hospital for 48 hours in order to have their blood pressure checked twice a day for two days and to have a urine analysis for glucose performed before discharge.

11. AT ENROLMENT

At enrolment the parents/ guardians will be given their copy of a 'fit diary'. Its use, and how to complete it, must be explained and fully understood. In addition the importance of this diary to interpreting the results of the trial should be explained. Details of the child's name, date of birth, address, NHS number, trial number, consultant and general practitioner should be completed. In addition we will ask all parents/guardians for a third party address (e.g. a grandparent) so that if they move and we lose contact with them we can try and track them through this third party. As a minimum, the parents/guardians will be expected to make a once daily entry for the first 4 weeks of the trial and a once weekly entry thereafter, until the time of the final developmental assessment (12 -14 months), with a final 7 day daily entry for those still having seizures. They should bring the diary with them to all clinic appointments and they may use the diary to record more detailed information if the lead clinician so wishes.

12. BEFORE DISCHARGE

Before discharge please arrange for a follow up EEG as close to 14 days after the start of treatment as possible. Please also see the child in out-patients as close to 14 days after the start of treatment as possible (but not less than 14 days after the start of treatment).

13. FOLLOWING DISCHARGE, DURING THE INITIAL TWO-WEEK PERIOD

Once the patient is discharged from hospital, if on steroids the blood pressure and urine analysis for glucose should be performed weekly whilst treatment continues, until the dose is reduced when this may be omitted if problems have not already been detected.

14. RESPONDERS AND PROPOSED TREATMENT FOR RELAPSE

Responders: are those in whom there is total cessation of spasms for at least 48 hours up to and including the end of the 14th day of treatment.

Relapse: a single spasm in a responder constitutes a relapse.

If a child relapses within the initial 2-week period then the lead clinician would be expected to increase the dose of the initial therapy up to the maximum recommended dose as per protocol.

If for any reason the lead clinician felt that it was not in the child's best interest to increase the dose of initial therapy (for example side effects experienced) then he should inform the trial centre as soon as possible, preferably but not necessarily before changing therapy.

15. REVIEW AT 2 WEEKS

Please review the patient as close to 14 days after the start of treatment as possible but not less than 14 days after the start of treatment. The patient should be seen in order to confirm their progress and to complete the brief standardised progress report form. If the infant has responded the patient will continue on the same therapy as above.

16. NON-RESPONSE AT 2 WEEKS

The trial will be analysed by intention to treat at randomisation. However, in order to minimise the effects of a multitude of different subsequent treatments, we will ask, but not require, clinicians to change to the alternative treatment (see below) if the primary treatment fails. If a response has not occurred after 2 weeks, we expect the lead clinician to change to the alternative therapy i.e. either steroids after vigabatrin (the lead clinician to choose which steroid - Synacthen Depot or prednisolone) or vigabatrin after steroids. This alternative treatment will continue for the third and fourth weeks (a full 14 days) at the same dose as recommended for the first two weeks. If the lead clinician does not feel that this treatment is in the child's best interest they may change to a treatment of their own choice without violating the trial protocol, but they should notify the trial centre of this change in treatment plan using the 14 day standard report form. If both treatments fail, the clinician will be left to choose the most appropriate treatment.

17. RELAPSE AFTER THE INITIAL TWO-WEEK PERIOD

The lead clinician may choose his own treatment, but we suggest if the child relapses

after the initial two week period either: If on vigabatrin increase the dose in parallel with the child's weight gain (if increase is more than 1 kg) or if on 100 mg/kg/day increase to 150 mg/kg/day; If on steroids repeat the course once even if tailing. If these measures fail after a full 14 days treatment change to the alternative therapy i.e. either steroids (Synacthen Depot or prednisolone) after vigabatrin, or vigabatrin after steroids.

18. SIDE EFFECTS

Should an infant suffer unacceptable side effects then the treatment should be discontinued and the trial centre informed immediately. The lead clinician may choose his own alternative treatment, but we suggest the lead clinician change to the alternative therapy i.e. either steroids (Synacthen Depot or prednisolone) after vigabatrin, or vigabatrin after steroids.

19. SUBSEQUENT FOLLOW-UP

All enrolled infants should be seen at 3 monthly intervals as a minimum although we realise that many will be seen more often because of their clinical need. The lead clinician will be asked to fill in a brief progress report form to send back to the trial centre in Bath at each 3 monthly visit until the 12 - 14 month assessment. Psychomotor development will also be assessed using a telephone questionnaire based on the "Vineland Adaptive Behaviour Scales" (see section 26). This will be done by a trained researcher who will be based in Bath when the infant is between 12 and 14 months of age.

20. RECRUITMENT RATE

This is a national study and it is hoped to recruit all new cases of infantile spasm in the United Kingdom occurring within the study period. Papers dealing with the epidemiology of infantile spasms put the incidence between 1 in 2380 and 1 in 6250 births. The average UK birth rate is approximately 800,000 per year. Therefore, it should be possible to recruit between 130 and 340 new cases per year. Taking into account exclusions, recruitment should be completed within 18 months. We intend to drive recruitment actively and have already sought to recruit one paediatric neurologist from each old health region to help promote the study. The trial centre will take responsibility for ethics committee approval for each district in the UK and will recruit one paediatrician from each district to help promote the study. We will provide coasters and post-its printed with contact arrangements at the commencement of the trial. A newsletter will be sent to all recruiting clinicians and all promoters every 2 months. We will notify all EEG departments of the trial with coasters, post-its and newsletters and ask them to remind clinicians of the trial whenever a request is made for an EEG in a child with possible infantile spasms, or whenever hypsarrhythmia is found.

21. COMPLIANCE

This is a serious disorder with profound sequelae. The motivation for clinicians and parents of patients to participate in treatment is high. The clinical workload to be imposed on attending physicians is little more than constitutes good clinical practice. (The workload to be imposed on parents is small). The administrative work will be

kept to a minimum - we will not collect unessential data and the trial centre will be responsible for documentation and for submissions to ethics committees.

22. LIKELY RATE OF LOSS TO FOLLOW-UP

Loss to follow-up should be small. Patients known to be likely to move outside the country during the trial period will be excluded at entry. As this is a national study, movement within the UK should not lead to loss of contact. The patient's NHS number, general practitioner and a third party address (e.g. grandparents) will be recorded on entry to the trial thus making it easier to keep track of patients who move.

23. POST-RANDOMISATION STRATIFICATION

There will be post-randomisation stratification for potential confounding variables not accounted for in pre-randomisation. These include EEG appearance (i.e. hypsarrhythmia vs atypical vs normal awake, normal asleep) and diagnostic sub-groups (i.e. cerebral dysgenesis on cranial scanning, chromosomal abnormalities or other syndromes and other diagnosis such as metabolic disease). Social factors will include birth order and maternal age at school leaving.

24. POST-INVESTIGATION DIAGNOSTIC SUBGROUPS

It may be possible to see if any trends in outcome are repeated within subgroups of the trial population. The largest subgroup should be infants where development was delayed (as shown by pre-randomisation stratification data and as shown separately by the developmental history. Smaller subgroups, e.g. those diagnosed with cerebral palsy on clinical examination, cerebral dysgenesis on cranial imaging, normal awake and asleep EEGs, are unlikely to be large enough for separate analysis. However, the data will be examined in case there is a dramatic difference in outcome, or a consistent trend.

25. PRIMARY OUTCOME MEASURE

The primary outcome measure will be the number of patients who achieve complete cessation of spasms for at least 48 hours up to and including the end of the 14th day of treatment.

26. SECONDARY OUTCOME MEASURES

1. Time taken to complete cessation of all spasms for at least 48 hours.
2. Partial response i.e. those patients that have a reduction in the number of spasms during the two week period.
3. Relapse rates.
4. Other seizure types and frequency at 14 months, in those still having seizures.
5. Resolution of hypsarrhythmia at 14 days.
6. Developmental progress at 12–14 months of age. This will allow at least 2 months of recovery following treatment and is an age at which some language development has occurred. It is believed that delaying the assessment to a

greater age will give little advantage and would have the disadvantage of increasing the impact of environmental factors.

The Vineland Adaptive Behaviour Scales have been developed and validated in the U.S.A. to measure "adaptive behaviour" defined as the performance of the daily activities required for personal and social sufficiency. It concentrates on the usual response, not the best response to any task. It has been validated in greater detail on larger numbers of children (3000) and has been used in the U.K. for other developmental follow-up studies. It achieves construct validity, content validity and has been compared to other scales in both normal and handicapped children. It has been shown to have internal consistency, test-retest and interrater reliability. It has been designed to minimise the influence of physical handicap.

The Vineland has four domains (communication, daily living skills, socialization and motor skills) and these combine to give an Adaptive Behaviour Composite: each of these has a standard score of 100 with a standard deviation of 15 and each can be expressed as an age equivalent (developmental age).

The Vineland scales can easily be adapted to be performed as a parental questionnaire that can be administered over the phone.

27. ANALYSIS

Assuming recruitment of 250 children over the 18 month period, with approximately 125 randomised to vigabatrin and 125 to "steroids", assuming approximately 50% will achieve cessation of seizures in the "steroid" group, the trial will have 90% power to detect an improvement in cessation of seizures to 70% in the vigabatrin group. We are aware that the pattern of developmental age in the two groups may be bimodal. A direct comparison of the developmental age (total score and subsets) of the two groups will be undertaken, but we will also determine the proportion of individuals in each group whose development is one, two and three standard deviations below the mean for the Vineland.

B.2 Study protocol amendment 11 May 2000

This information sheet for parents or guardians was a study protocol amendment approved by the MREC on 11 May 2000.

UKISS – Extra information for parents or guardians: 11 May, 2000

The UKISS study was approved by a Multicentre Research Ethics Committee in September 1998. Since then, it has been approved by more than a hundred local research ethics committees. Several of those committees suggested how we might make these information sheets clearer. We have also had useful comments from other doctors, and from some NHS managers. We have written this update to make you aware of these suggestions. We hope that you will find it useful.

Reason for doing the study. One part of the information sheet was intended to explain the reason for doing the study. This is the paragraph that begins: "If we do not do this study

we will never learn which treatment is best." Some research ethics committees thought that this paragraph might seem coercive. In other words, it might seem to put pressure on you to allow your child to join the study. We do not wish to put pressure on you. Our aim was to explain the reasons for doing the study. We apologise if this part of the information sheet gave the wrong impression.

Leaving the study before it is finished. You may take your child out of this study at any time and for any reason. You do not have to explain your reasons to your doctor or to anyone else, and your decision will not affect the care your child receives. This fact is written on the consent form. However, it does not appear on the information sheet. It is important that you are aware of this right.

Getting more advice. Some Local Research Ethics Committees asked us to print their address and phone number, or that of the local Community Health Council. Please note that you can obtain advice from either of these bodies. You may also tell them any concerns or worries you have about the study. You can get the addresses or phone numbers for these bodies from several places. Try your local telephone directory; your local hospital; or your local area health authority.

What if something goes wrong? If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms may be available to you.

Extra information about vigabatrin. Since the study was first approved, more studies about vigabatrin have been completed. In 1997, some adult patients who had been treated with vigabatrin were found to have problems with vision. This problem was poor vision around the outside of the visual field. It is called a 'visual field defect' or 'visual field constriction'. Many people are not aware that they have this type of visual field defect, and it is often only found when we do special tests of vision. Such tests have now been done on many people who have been treated with vigabatrin. These tests suggest that the problem occurs in about one in three people who have been treated for more than six months. It has been found in a small number of older children. We are not able to do these tests in babies or children less than nine years old, so we do not know if they are at risk from this side effect. Vigabatrin has been reviewed by the 'European Committee for Proprietary Medicinal Products'. This committee has members from all countries in the European Community, and it considers drug licences and drug safety. This review decided that vigabatrin may still be used to treat infantile spasms.

Description of prednisolone. Some of the research ethics committees commented on our description of prednisolone. We said that it is a 'type of steroid that our bodies produce naturally'. We would like to make it clear that prednisolone itself is not produced in the human body. It has a structure that is slightly different from steroids that are produced in the body. However, its actions are like those of steroids that the body makes every day, and which are made in higher doses when the body is stressed or ill. A better description is that prednisolone is "similar to a type of steroid that our bodies produce naturally". We hope that this description is clearer.

Dose of prednisolone. Some doctors have commented that the dose of prednisolone is higher than they usually use. We know that drugs such as Synacthen Depot cause the adrenal gland of the body to make very high doses of the body's natural steroids, and we think that prednisolone might be a better treatment if given at a higher dose. Some doctors use steroids

for several months. However, other doctors have suggested that shorter courses of treatment are safer. It is possible that the higher dose may cause more side effects. However, we hope that the higher dose and shorter length of treatment will be both better and safer.

Steroids and immunisations. The information sheets for prednisolone and Synacthen® Depot say that your child should not receive immunisations (vaccines) during treatment. Please note that the British National Formulary – the general guide to prescribing medicines in the UK – recommends that some immunisations are better avoided for three months after treatment. However, this needs to be considered in the light of your child's needs. If your child is given prednisolone or Synacthen® Depot, please ask your doctor about this.

Summary. We hope that this extra information is useful. Please ask your doctor if you would like more explanation about any of these issues. Thank you for taking the time to consider joining the study.

B.3 Study protocol amendment 30 April 2001

This information sheet for parents or guardians was a study protocol amendment approved by the MREC on 30 April 2001. It is identical to the earlier protocol amendment shown in Section B.2 with the exception of the paragraph on *Dose of prednisolone*, which was broadened into the paragraph shown below on *Safety of prednisolone and Synacthen® Depot.*

UKISS – Extra information for parents or guardians: 30 April 2001 (incorporates and replaces extra information sheet 11 May, 2000)

Safety of prednisolone and Synacthen® Depot. Some doctors have commented that the dose of prednisolone is higher than they usually use. We know that drugs such as Synacthen® Depot cause the adrenal gland of the body to make very high doses of the body's natural steroids, and we think that prednisolone might be a better treatment if given at a higher dose. Some doctors use steroids for several months. However, other doctors have suggested that shorter courses of treatment are safer. Treatment with prednisolone or Synacthen® Depot may mask the signs and symptoms of infection. It may also make your child less able to fight infections. If your child becomes unwell or develops fever while taking either of these treatments, please phone your doctor for advice. Your child may need urgent treatment with antibiotics. Chicken pox is more dangerous to children on steroids and if your child comes into contact with chicken pox while on steroids, or shortly afterwards, you must immediately inform your consultant. Treatment for chicken pox is available. It is possible that the higher dose may cause more side effects. However, we hope that the higher dose and shorter length of treatment will be both better and safer.

Appendix C

Questions and Statements from West Delphi

In this thesis, references to questions and statements from West Delphi rounds are referred to by abbreviations of the form R1Q5, for example, to refer to West Delph round 1 question 5; and R4S1 to refer to round 4 statement 1.

C.1 Round 1 invitation

C.2 West Delphi round 1 questions

R1Q1. The clinical features of infantile spasms are well established, and I have no problem in deciding when a child has this condition: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R1Q2. I think that we should diagnose infantile spasms only if onset of symptoms occurs: (a) before 1 year of age; (b) before 2 years of age; (c) before 5 years of age; (d) I am not sure if we should have an upper age limit; (e) I think that we should NOT have any upper age limit.

R1Q3. It is easy to decide, at the time of diagnosis of infantile spasms, whether a child had developmental delay that preceded the onset of spasms: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R1Q4. The traditional categorisation of infantile spasms into symptomatic and cryptogenic/idiopathic groups is a useful way of predicting developmental prognosis: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R1Q5. It is clear when a child has idiopathic rather than cryptogenic infantile spasms: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R1Q6. Identifying EEG features that are necessary and sufficient to define hypsarrhythmia for studies of infantile spasms is too complicated and ambitious for this Delphi process: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree

strongly.

R1Q7. Aggregated data from studies such as meta-analyses are likely to help me make treatment decisions for my own patients with infantile spasms: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R1Q8. We need to standardise the idea of "cessation of spasms" in studies of infantile spasms by requiring that no spasms are witnessed for a minimal period of: (a) 24 hours; (b) 48 hours; (c) 1 week; (d) 2 weeks; (e) 1 month; (f) a minimal period different from those above; (g) it makes no sense to have such a minimal period.

R1Q9. If a study reports that some children developed hypertension, it is clear to me that these have been serious adverse events: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R1Q10. We should make a strong recommendation that studies of infantile spasms include an assessment of development at least as late as: (a) 12 months; (b) 24 months; (c) 36 months; (d) 5 years; (e) 12 years; (f) I do not think that such developmental assessments should be required.

C.3 West Delphi round 2 questions

SECTION 1

R2Q1. Please indicate amendments, additions or deletions you would make to this general overview statement about infantile spasms. Try to keep the statement short, so that it provides a succinct description of infantile spasms.

> STATEMENT: "Infantile spasms is a form of epilepsy that usually has an onset in children less than two years old. Its main clinical manifestation is epileptic spasms, which usually occur in clusters. There are many potential etiologies since it is associated with many conditions. The most characteristic EEG finding is hypsarrhythmia. This is found in most cases, but not throughout the clinical course of the condition. Hypsarrhythmia is usually suppressed during a clinical attack of epileptic spasms. This suggests that, although there is EEG evidence of widespread dysfunction of the cerebral cortex, the actual epileptic spasms originate from the cerebral subcortex."

R2Q2. We might wish to use distinct terms to define the following clinical scenarios: (a) the syndrome of clinical spasms with hypsarrhythmia; (b) clinical spasms with epileptiform EEG features but no evidence of hypsarrhythmia; (c) clinical spasms with no evidence of EEG abnormality; (d) hypsarrhythmia with clinical spasms that occur singly but never in clusters; (e) hypsarrhythmia with no observed clinical spasms f) cases with clinical spasms that have not yet had an EEG; (g) the spectrum of conditions with clinical spasms.

Please suggest succinct and distinct terms or phrases for these entities (though you may prefer a single term for (f) and (g)).

R2Q3. Cases of infantile spasms with tuberous sclerosis (TS) seem to show substantially better treatment responses to vigabatrin than other symptomatic cases. This suggests that it would be useful to have a diagnostic or prognostic classification of infantile spasms based on different

etiologies. There is a balance between having too few groups and failing to investigate important differences, and having too many groups and leaving studies prone to small number biases. Etiologic classes would ideally reflect similarities in: underlying mechanisms (about which little is known); prognosis; and treatment responses.

Please suggest a system of etiologic classes that might meet these needs. For example, you might suggest 3 classes: (1) non-symptomatic cases; (2) cases with TS; (3) symptomatic cases other than TS. Or you might suggest 7 or 8 classes.

R2Q4. Please state your opinion on what are necessary EEG features of hypsarrhythmia. Necessary features are those which, if not present, would make you decide that the EEG is NOT hypsarrhythmic. These should be single features: for example, "high amplitude slow waves" (or preferably something more specific, such as, "slow waves with amplitude greater than 200 microvolts"). If you can imagine calling an EEG hypsarrhythmic in the absence of this feature, it is not a necessary feature.

R2Q5. Please state your opinion on what are sufficient EEG features of hypsarrhythmia. Sufficient features are likely to be clusters, such as "high-amplitude, multifocal, epileptiform spikes, with temporal variation in spike location and duration." There may be several different clusters or patterns that you would consider sufficient to constitute hypsarrhythmia. Note that, if you have defined a necessary feature, this would need to occur in each cluster of sufficient features. For example, if you had stated "high-amplitude slow waves" as a necessary feature, this feature should appear in each cluster of sufficient features. If you can imagine calling an EEG with all these features something other than hypsarrhythmia, it is not a cluster of sufficient features.

R2Q6. State any arguments you may have in favor of or against the choice of a 28-day spasm-free period to determine the outcome *cessation of spasms*. These arguments will inform a vote in Round 3 of West Delphi.

R2Q7. Please state which test(s) of development or function you would wish to perform on a child who had had infantile spasms and was now aged 5 years. If you know of an analogous test in English, please state that also.

ROUND 2 SECTION 2

Please indicate your preferred responses to these questions as in ROUND 1.

R2Q8. A clinical diagnosis of infantile spasms should only be made when some of the spasms occur in clusters. (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q9. The most appropriate ictal unit (or seizure unit) is: (a) The spasm; (b) The cluster of spasms; (c) I am not sure which of these ought to be the ictal unit; (d) I think another measure should constitute the ictal unit; (e) I do NOT think the concept of an ictal unit is useful.

In the following question, please rank your responses according to which you believe to be most important.

R2Q10. It is important to have an age-related classification of infantile spasms because: (a) older and younger cases are more likely to be misclassified cases of other conditions; (b) there is a substantially different etiologic case-mix; (c) age at onset is an independent predictor of prognosis; (d) age-related pathophysiological mechanisms are likely to result in different re-

sponses to treatment; (e) other [please state].

R2Q11. We should classify cases of infantile spasms by age at onset: (a) into 3 classes: (i) age less than 3 months (early); (ii) age 3 to 12 months (classic); and (iii) age over 12 months (late); (b) into 4 classes: (i) age less than 3 months (early); (ii) age 3 to 12 months (classic); (iii) age 12 months to 24 months (late); (iv) age over 24 months (very late); (c) into classes different from the above [please state]; (d) into one of the above classifications but referring to them by different terms [please state]; (e) I do NOT think that an age-related classification is worthwhile.

R2Q12. With respect to an age-related classification of infantile spasms, age at onset is likely to be assessed unreliably, and age at diagnosis is a better age-related variable: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q13. With respect to an age-related classification of infantile spasms, we should adjust for the effect of gestational age at birth (preterm delivery): (a) at all ages; (b) for children up to the age of 2 years; (c) for children up to the age of 1 year; (d) for children up to the age of 3 months; (e) I am not sure if we ought to use age adjustment; (f) we do NOT need to use ages adjusted for gestational age at birth.

R2Q14. Since developmental delay at the time of onset of infantile spasms is hard to assess, many cases are likely to be misclassified and we ought NOT to use this as a criterion for defining West syndrome: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q15. Developmental delay at the time of diagnosis is likely to be an independent predictor of prognosis after adjustment for the effect of underlying cause: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q16. We should distinguish prospective classification of infantile spasms (ie, classification soon after diagnosis and before a treatment decision is made) from retrospective classification (ie, classification after we have performed a full set of investigations): (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q17. The term *cryptogenic infantile spasms* should no longer be used: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q18. It is easy to clinically distinguish myoclonus from spasms: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q19. Spasms can be reliably distinguished from myoclonus and tonic seizures by the duration of EMG potentials: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q20. It seems likely that the ictal episodes associated with infantile spasms have a subcortical origin: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q21. West Delphi should consider the diagnostic and therapeutic role of pyridoxine in infantile spasms: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

The next question refers to: Engel J, Jr. A Proposed Diagnostic Scheme for People with Epileptic Seizures and with Epilepsy: Report of the ILAE Task Force on Classification and Terminol-

ogy. *Epilepsia* 2001;**42**:1–8. This suggests five diagnostic axes: Axis 1 – Ictal phenomenology; Axis 2 – Seizure type; Axis 3 – Syndrome; Axis 4 – Etiology; Axis 5 – Impairment.

R2Q22. West Delphi should attempt to develop a classification scheme for infantile spasms that is consistent with the 5-axis diagnostic system proposed by the ILAE Task Force on Classification and Terminology: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q23. In future studies of infantile spasms, the primary outcome should be *cessation of spasms*: (a) I agree strongly; (b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I disagree strongly.

R2Q24. Please rank the following outcomes: (a) time to cessation of spasms; (b) time to 50% reduction in number of ictal units; (c) relapse; (d) serious adverse events; (e) non-serious adverse events; (f) development at 2 years of age; (g) development at 5 years of age; (h) progression to other seizure types.

In the following question, please indicate as many responses as you think appropriate. You may wish to comment on which terms we might use for such relapses.

R2Q25. In a child that has had cessation of spasms by an agreed definition, the occurrence of the following features should be considered a form of *relapse*: (a) spasms occurring in clusters; (b) spasms that do NOT occur in clusters; (c) a single witnessed spasm; (d) epileptic movements that are not spasms; (e) hypsarrhythmia on an EEG without any clinical seizure activity; (f) an epileptiform EEG that does not show hypsarrhythmia; (g) an abnormal EEG with no epileptiform features.

In the next question we consider the *period of sufficient therapeutic trial*. This is the period within which you would reasonably expect a treatment response (for example, no further observed spasms). You would expect most cases to have responded within this period. If the treatment has not been effective within this period, you would consider it unlikely that the child will respond to this treatment and you would change to another treatment regimen.

R2Q26. The most appropriate period of sufficient therapeutic trial for treatments of infantile spasms is: (a) 5 days; (b) 7 days; (c) 10 days; (d) 14 days; (e) 21 days; (f) 28 days; (g) other [please state]; (h) this would vary from treatment to treatment and we ought not to attempt to recommend a standard.

In the next question we will consider the *period of necessary therapeutic trial*. This is the period within which you would not expect a treatment response (for example, no further observed spasms). Few cases would have responded to treatment by the end of this period. If the treatment has not been given for this period, you would consider that the treatment had not had a *fair therapeutic trial*. (Of course, if there were an adverse event, it might be necessary to stop the treatment before the end of this period.)

R2Q27. The most appropriate period of necessary therapeutic trial for treatments of infantile spasms is: (a) 2 days; (b) 3 days; (c) 5 days; (d) 7 days; (e) 10 days; (f) 14 days; (g) other [please state]; (h) this would vary from treatment to treatment and we ought not to attempt to recommend a standard.

R2Q28. With respect to developmental assessment of children with infantile spasms, we should adjust for the effect of gestational age at birth (preterm delivery): (a) at all ages; (b) for children assessed at the age of 5 years; (c) for children assessed at the age of 2 years; (d)

for children assessed at the age of 1 year; (e) for children assessed at the age of 3 months; (f) I am not sure if we ought to use age adjustment; (g) we do NOT need to use ages adjusted for gestational age at birth.

R2Q29. The most appropriate single age for early developmental or functional assessment of children who have had infantile spasms is: (a) 12 months; (b) 14 months; (c) 18 months; (d) 24 months; (e) 36 months; (f) other.

R2Q30. POTENTIAL CONSENSUS STATEMENT: We recommend that developmental assessments of children who have had infantile spasms are made at least as late as the age of 5 years, and we encourage further assessments at the age of 12 years. (a) I strongly agree; 9b) I agree; (c) I am not sure if I agree or disagree; (d) I disagree; (e) I strongly disagree.

SECTION 3: GENERAL COMMENTS ON THIS ROUND

SECTION 4: COMMENTS ABOUT FUTURE ROUNDS

C.4 West Delphi round 3 questions

Round 3 will consist mainly of potential consensus statements that you are invited to criticise and comment upon. Responses to these potential consensus statements will generally be of the form: "(a) I generally agree with this statement; (b) I am not sure about this statement; (c) I disagree with this statement, and my reasons are ... comments, including whether you think a statement about this area of study design should be included in the West Delphi consensus." It is not necessary to state any reasons for disagreeing with the statement, but it helps the process if other participants know why there is disagreement. Also, we need as a group to address the underlying reason for the disagreement when we formulate questions for the next round.

In order to assess the value of a potential consensus statement, it might be useful to ask the questions such as:

- If I were designing a study of treatments for infantile spasms, would this recommendation or statement make my task easier?
- If I were trying to classify a child who presents to me with what look like infantile spasms, would this scheme be useful and valid?
- Is this statement consistent with other statements with which I agree?
- If I were reading several papers on infantile spasms, would my task be easier if I knew that the authors had used definitions from this consensus?

In this round, we will start to address proposals for how outcome measures might best be reported. These have been incorporated into the statements and are open to debate and criticism.

Notes on flow chart shown in figure 5.1 on page 189 and to accompany R3Q1.
"*EEG: standard, sleep and video EEGs are all performed, as necessary, before excluding a positive finding.
"**2 years: 2 years is not an absolute upper limit, but substantially older cases would be classified as another syndrome, such as that of periodic spasms.

"Suggested cross-reference to ILAE multiaxial classification: Axis 1 (ictal phenomenology) = spasms; Axis 2 (seizure type) = epileptic spasms; Axis 3 (syndrome) = West syndrome, infantile spasms and IS-SS variant.

"Suggested use for syndrome terms: 1) Studies of infantile spasms would include cases of IS-SS variant and cases of West syndrome unless exclusions or restrictions are explicitly stated; 2) Studies of West syndrome would exclude cases without clustered spasms and cases without hypsarrhythmia.

"Note that this classification requires clusters of spasms for a diagnosis of West syndrome. Cases with spasms occurring singly and without any witnessed clusters, even when associated with hypsarrhythmia, are not classified as West syndrome. Thus, using this classification, West syndrome becomes effectively a triad: spasms; occurrence of those spasms in clusters; and hypsarrhythmia."

R3Q1: a) I generally agree with the content of the above flow diagram; b) I am not sure about the content of this flow diagram; c) I think this flow diagram would be better if ....

Notes on flow chart shown in figure 5.2 on page 190 and discussed in R3Q2.

"It is well known that hypsarrhythmia can occur in the absence of spasms, and sometimes without any evident clinical seizure [236]. Since hypsarrhythmia is effectively the presenting feature in such cases (at least, with respect to considering a diagnosis of infantile spasms) it is useful to have a scheme for classification conditional upon the presence of hypsarrhythmia."

R3Q2: a) I generally agree with the content of the above flow diagram; b) I am not sure about the content of this flow diagram; c) I think this flow diagram would be better if ....

The following questions relate to the reports of the ILAE Task Force on Classification and Terminology *Proposed Diagnostic Scheme for People with Epileptic Seizures and Epilepsy* and the *Glossary of Descriptive Terminology for Ictal Semiology* [233, 234].

R3Q3. Statement: "We propose that studies of infantile spasms use the method of classification and description proposed by the ILAE Task Force on Classification and Terminology, 2001, which uses a 5-axis system of classification [233]."

R3Q4. Statement: "With respect to the *Glossary of Descriptive Terminology for Ictal Semiology, 2001*, we prefer to drop the adjectival component of the term epileptic spasms since, from the description of the ictal phenomena alone, it is impossible to infer that the spasms are epileptic in nature. Thus, we prefer to refer to the ictal phenomena as *spasms* [234]."

R3Q5. Statement: "With respect to Axis 1 (ictal phenomenology), we propose the term *spasms* for the ictal phenomena of infantile spasms or West syndrome. The spasms normally involve the trunk and proximal limbs. They may involve only the trunk and may manifest as merely a head nod. The subtlest manifestation would be a facial grimace [237]. Spasms would not usually involve only the limbs, and this feature would suggest myoclonus or another seizure type. Asymmetric spasms are consistent with a diagnosis of infantile spasms or West syndrome, and the presence of features such as this should be included in the Axis 1 description."

R3Q6. Statement: "There have been descriptions of more subtle forms of behavioural accompaniment to what appears to be the attack associated with a hypsarrhythmic EEG. These include episodes of gasping and isolated eye movements [237]. We recommend that, though they may be the ictus in some children with hypsarrhythmia, such subtle forms are not classified as spasms. Such movements are not suggested by the term spasms, are difficult to detect

clinically and, because of their subtlety, would not be reliable outcomes in clinical studies."

R3Q7. Statement: "With respect to Axis 2 (seizure type) of the ILAE proposed diagnostic scheme, we propose that the term *epileptic spasms* is used to describe the episodes of brief muscular contraction, generally with a duration of approximately 1 second: that is, longer than an episode of myoclonus, and shorter than a tonic seizure. This term would include the *period spasms* of Gobbi and *infantile spasms* [25, 29]. The term *epileptic spasms* implies that the EEG is consistent with the diagnosis of an epilepsy, but does not imply any more specific EEG pattern."

R3Q8. Statement: "With respect to Axis 3 (syndrome) of the ILAE proposed diagnostic scheme, we propose that *infantile spasms* is the syndrome of epileptic spasms with onset generally during the first two years of life in association with focal or diffuse interictal EEG abnormalities [25]. We propose that *West syndrome* is defined by the association of infantile spasms, at least some of which occur in clusters, with an interictal EEG showing hypsarrhythmia. This may be either typical hypsarrhythmia, or hypsarrhythmia with atypical features." [Please note that we would therefore be proposing two terms for inclusion in this axis: infantile spasms and West syndrome.]

R3Q9. Statement: "We see no reason for including developmental delay at the time of onset as a defining feature of West syndrome. Indeed, developmental delay at onset of spasms is likely to be assessed unreliably because spasms are often subtle and unrecognised at their true time of onset, and because development is hard to assess in early infancy. This would be likely to lead to misclassification of cases."

R3Q10. This question relates to the abstract from the ICD-10 paediatric adaptation [similar to the version included in the final consensus statement that is shown in table 5.15 on page 199]. Statement: "We propose that Axis 4 (etiology) of the multiaxial classification system, when used for studies of infantile spasms, should use a classification that concords with the WHO ICD-10 paediatric adaptation. Cases that cannot be classified into any of these groups would be classified as *idiopathic*. Studies might undertake separate analyses of etiologic subgroups, or aggregations of these subgroups, when there exist *a priori* reasons for suspecting different response from such groups. Standardised classification by this method would facilitate *a posteriori* analyses of etiologic groups using data aggregated from many earlier studies."

R3Q11. "With respect to Axis 5 (impairment), we should explore the use of classes obtained from the WHO IDIDH-2 classification."

R3Q12. Statement: "Infantile spasms typically have an onset between 3 and 12 months of age. Younger and older children are more likely to have other conditions, and there is a greater risk of misclassification. Also, age at onset of spasms may influence outcomes. We propose that studies of West syndrome and infantile spasms report outcomes for children in the age groups: 1) less than three months of age (corrected for preterm delivery); 2) 3 months (corrected age) and up to 12 months of age; 3) 12 months of age and older. We propose that these be referred to respectively by the terms: *early onset*, *classic onset*, and *late onset*. Onset would rarely occur after two years of age, but it is biologically implausible to set an absolute upper age limit."

R3Q13. Statement: "In studies of infantile spasms, the terms *symptomatic*, *cryptogenic*, and *idiopathic* have been used variably and often without explicit definition. The recent task force diagnostic scheme proposes that the term *probably symptomatic epilepsy syndrome* is used, in place of the former term *cryptogenic*, to describe syndromes in which there is no identified

etiology but where there is thought to be an underlying structural brain lesion (ie, a symptomatic epilepsy syndrome) [233]. It proposes the term *idiopathic epilepsy syndrome* to describe syndromes with epilepsy and no underlying brain lesion; no other neurologic symptoms or signs; an age-dependent course; and a presumably genetic etiology."

R3Q14. Statement: "With respect to etiologic classification, we propose that studies state clearly the etiologic status of participants at the time of the treatment decision and at the end of the study. We suggest the qualifying term *prospectively* to indicate the etiologic class status of participants at the time of treatment decision (and to refer to this as the *prospective etiologic classification*), and the unqualified terms *symptomatic, probably symptomatic,* and *idiopathic* to indicate the etiologic status of participants at the end of the study or at the time of the most recent assessment (and to refer to this as the *final etiologic classification*). One might expect a large proportion of prospectively probably symptomatic study participants to later become symptomatic, and the same for a smaller proportion of prospectively idiopathic participants. Prospectively symptomatic participants ought all to end the study as symptomatic."

R3Q15. Statement: "With respect to etiologic classification, we propose that the final etiologic classification is used for analyses when the primary study question is related to efficacy and biological mechanisms; and that the prospective etiologic classification is used for analyses when the primary study question relates to effectiveness and treatment decisions. The prospective etiologic classification, which provides information about prognosis and that informs future treatment decisions, should not be regarded as inferior to the final etiologic classification, but merely serves different purposes. We recommend that studies clearly report reclassification of cases between prospective and final etiologic classes."

R3Q16. Statement: "We propose that, in studies of infantile spasms and West syndrome, the classification of cases as *symptomatic* or *probably symptomatic* should be extended beyond structural brain abnormalities to include cases with underlying chromosomal and metabolic etiologies that do not have evident structural brain abnormalities."

R3Q17. Statement: "With respect to the term *hypsarrhythmia,* we propose that this term is used to describe an EEG pattern that is characterised by random, high-voltage spikes and slow waves. The most striking features of hypsarrhythmia are: high-voltage (generally $> 200\,\mu V$) slow waves; spikes and waves from many foci and varying with time; a lack of synchrony and "chaotic" appearance. The typical appearance is more likely to be found in earlier stages of the disorder and when onset occurs at a younger age. The hypsarrhythmic pattern may disappear during REM sleep, but it may be found with greater sensitivity in some other stages of sleep [66]."

R3Q18. Statement: "With respect to the use of the terms modified hypsarrhythmia [67] and atypical hypsarrhythmia [32], we endorse the recommendation of the 1991 workshop on infantile spasms (Commission on Pediatric Epilepsy of the International League Against Epilepsy 1992 [28]) that study participants with typical and modified hypsarrhythmia are not reported in dichotomised groups but that, where appropriate, individual atypical features are described. The presence of atypical features may depend upon the stage of infantile spasms at which the EEG is performed; it may depend upon treatment; and it probably has little practical significance in randomised studies."

R3Q19. Statement: "We endorse the statement by the ILAE Commission on Outcome Measurement in Epilepsy, 1994-97 final report that 'there is a great need for standardization of

reporting research results [238].' We commend these aims and recommend them to those who embark on studies of infantile spasms."

R3Q20. Statement: "We recommend to those designing, analysing, interpreting, and utilizing studies of infantile spasms that consideration is given to the distinction between *efficacy* and *effectiveness*. An efficacy study looks at an intervention in ideal circumstances and with selected patients. An effectiveness study looks at interventions involving typical or unselected patients in everyday circumstances and includes the effects of other biases, such as non-compliance and drug interactions [238, 190]. We can think of no general *a priori* reason for efficacy and effectiveness studies to report radically different outcomes and outcome measures. We propose a common standard of outcomes for all studies of infantile spasms; that researchers state clear reasons for preferring other primary outcomes; and that, if other primary outcomes are preferred, the consensus standard outcomes are instead reported as secondary outcome measures in order to facilitate future synthesis of data."

R3Q21. Statement: "There is disagreement about whether the appropriate ictal unit in studies of infantile spasms should be the *spasm* or the *cluster of spasms*. Most members of West Delphi thought that it was more appropriate to use the cluster of spasms as the ictal unit. However, we felt that there was limited value in outcomes that rely on measurement of ictal units, such as time to 50% reduction of spasms, or proportion of participants having a 50% or greater reduction in spasms."

R3Q22. Statement: "We propose that the primary outcome in studies of West syndrome and infantile spasms be cessation of spasms for a period of 28 days. The primary response need not require cessation of hypsarrhythmia or normalisation of the EEG, but persistence or recurrence of hypsarrhythmia in primary responders should be reported. We propose that the main outcome measure is the proportion in each treatment group that has been spasm-free for a period of 28 days by the end of study day 42 (that is, the proportion of study participants that are spasm-free at the end of study day 14 and remain spasm-free 28 days later). A useful and related variable is 'time to 28-day freedom from spasms', which is best presented in the form of an actuarial ('survival') curve."

R3Q23. Statement: "We propose that a video EEG (or, less preferably, another form of EEG that includes a period of sleep) is performed within seven days of study day 42 on study participants who appear to have responded to treatment: that is, it is performed between study days 35 and 49. This will permit detection of persistent hypsarrhythmia in the absence of spasms, and determination of the group with the secondary outcome freedom from spasms with associated resolution of hypsarrhythmia. Ideally, an EEG would also be performed, on participants who appear to have responded to treatment, soon after study day 14."

R3Q24. Statement: "We propose that studies of infantile spasms and West syndrome report development at 2 years of age as a primary outcome measure that complements cessation of spasms. We recommend reporting of a further developmental assessment at 5 years of age, and we encourage reporting of development at the age of 12 years. Studies should consider reporting both an assessment of behaviour and an assessment of intelligence."

R3Q25. "Studies of West syndrome and infantile spasms should report, as a baseline characteristic, the proportion of children in each treatment group who appeared to have developmental delay at the time of onset of spasms. However, it should be appreciated that the exact timing of onset of spasms and of any apparent developmental delay may be difficult to assess, and

that there is a high risk of misclassification of this characteristic."

R3Q26. Statement: "We propose that baseline characteristics should be reported for each treatment or intervention group, and that the variables reported should include factors that may be prognostic indicators. We propose: (1) etiologic class; (2) sex; (3) age at onset (median and range, and proportions in age categories); (4) gestation (proportion born preterm, and median gestation); (5) birthweight (median birthweight and proportion under 1500 grams); (6) preceding seizures; (7) concurrent and previous treatment with AEDs or steroids; (8) lead time from apparent onset of spasms to treatment (median and range); (9) presence of hypsarrhythmia. Attention should be drawn to large differences that might bias the results. However, we do not recommend routine reporting of P values for baseline characteristics in a randomised trial: it is illogical to state significance or to reject a null hypothesis that the difference occurred by chance when it is known that the data were generated randomly and the difference must have occurred by chance."

R3Q27. Statement: "We propose that treatments for infantile spasms and West syndrome should be considered to have had a sufficient therapeutic trial after 14 days. In general, it is necessary to give a treatment for 14 days before deciding that it has no treatment effect, but withdrawal should be considered sooner if there is an adverse effect of that treatment. We propose that any study that uses a different period of necessary and sufficient therapeutic trial should state a rationale or empirical evidence for that decision."

R3Q28. Statement: "We propose that pyridoxine should be given intravenously under simultaneous EEG monitoring as a therapeutic and diagnostic test for pyridoxine-dependent seizures. Clinical response should occur within minutes, and cessation of paroxysmal discharges should occur within hours [121]. The therapeutic trial need take no longer than six hours, and randomised trial treatments may then be given."

R3Q29. Statement: "We propose that at least the following outcomes and measures be reported, by intervention group, in studies of infantile spasms and West syndrome: (1) cessation of spasms [number and proportion with last witnessed spasm before the end of day 14 of treatment and with no spasms for 28 consecutive days thereafter]; (2) development at 2 years of age [median and ranges for tests chosen]; (3) deaths and other serious adverse events [numbers and descriptions of events]; (4) relapse [numbers and proportion of primary responders relapsing; proportion of whole intervention group (that is, including non-responders); and distributions of time to relapse (from time of response)]; (5) presence of and progression to other seizure types [numbers, proportions, and seizure types]; (6) non-serious adverse events [numbers, proportions, and description of events]; (7) resolution of hypsarrhythmia at days 14 and 42 of the study [numbers with hypsarrhythmia at start of study, at study day 14 and at study day 42; proportions, and types of EEG performed]."

R3Q30. Statement: "Time to cessation of spasms can be represented by actuarial curves and is a clinically useful outcome that might inform future study designs. We propose that it is permissible for studies to report, in addition to 'time to 28-days of spasm-freedom,' 'time to last witnessed spasm in primary responders.' This gives a useful and intuitive clinical measure."

R3Q31. Statement: "In general, in discussing results we would deprecate the use of reporting outcomes in conditional statements such as: 'Of those responding to treatment X, $x/(n-f)$ did so within y days.' This involves a silent right-censoring of data, and can give a misleading impression of greater or quicker treatment effect. We would encourage simpler, unconditional

statements such as: 'For treatment X, x/n responded by day y.' "

R3Q32. Statement: "The following should be considered to constitute a relapse of infantile spasms at any stage after a primary response has been obtained: 1) spasms occurring in clusters; and 2) spasms occurring singly but not in clusters. A single witnessed spasm would not be reliable and should not be classified as a relapse. Because primary response is defined by cessation of spasms, persistent or recurrent hypsarrhythmia should not be considered to be a relapse unless it is accompanied by witnessed spasms. However, the persistence or recurrence of hypsarrhythmia is reported as part of a secondary outcome measure."

C.5 West Delphi Round 4 questions

In round 4, we will provide an extended statement that may be regarded as a putative consensus statement. The statements are presented in numbered paragraphs, and we invite you to make comments by referring to these paragraphs. Please state: (1) If you do not agree completely with the content of the statement, and (2) If you think that the statement ought not to be included. Please make as full an explanation as possible for your opinions. We believe that we are nearing a final consensus, but it will be necessary to put further amendments to the whole group in round 5.

Draft West Delphi Group Consensus Statement (West Delphi Round 4)

R4S1: *Rationale and aims of West Delphi.* West Delphi is a consensus elicitation process that aimed to propose a series of definitions and standards for use in studies of infantile spasms. In particular, its aim was to provide clearer definitions of cases and etiologic subgroups, and to provide information about what are considered to be the most important outcomes and outcome measures. We hope that these standards will help those who wish to design future studies of infantile spasms, and that they will result in better information for doctors who wish to choose the best approach to treating infantile spasms.

R4S2: *Constitution of the West Delphi Group.* The West Delphi Group consists of doctors with an interest in infantile spasms and who agreed to participate in the email consensus elicitation process. Some of them have been involved in previous studies of infantile spasms, and others are interested in the clinical usefulness of information from studies. Many were recruited from those attending the international symposium on West syndrome and other infantile epileptic encephalopathies, Tokyo, February 2001. The final consensus statement has been agreed by X doctors from Y countries, and the names of participants are listed at the end of this paper.

R4S3: *Definition of infantile spasms (IS).* The West Delphi Group proposes that the term *infantile spasms (IS)* is used to describe a particular form of epilepsy that rarely has an onset in children over two years old and usually has onset in children under one year old. Its main clinical manifestation is clinical spasms that usually occur in clusters. There are many potential etiologies and infantile spasms are associated with many conditions. The most characteristic EEG finding is hypsarrhythmia. However, hypsarrhythmia is not found in all cases, nor is it found throughout the clinical course of the condition. Hypsarrhythmia is usually suppressed during a clinical attack of epileptic spasms. The spasms are often associated with developmental arrest or regression.

R4S4: *Definition of West syndrome (IS).* We propose use of the term *West syndrome (WS)* to mean the combination of spasms that occur in clusters and hypsarrhythmia on an EEG. We do not require, as have some previous definitions of West syndrome, that there is evidence of delayed development before the onset of spasms. The inclusion of the requirement for spasms occurring in clusters forms a new triad. West syndrome is the triad of: (1) clinical spasms; (2) spasms that occur in clusters; and (3) the presence of hypsarrhythmia on an EEG.

R4S5: *Developmental delay at onset of clinical spasms.* We see no reason for including developmental delay at the time of onset as a defining feature of West syndrome. Indeed, developmental delay at onset of spasms is likely to be assessed unreliably because spasms are often subtle and their true time of onset is often unrecognised, and also because development is hard to assess in early infancy.

R4S6: *Definition of infantile spasms single-spasm variant (ISSV).* It is less usual for infantile spasms to always occur singly rather than in clusters, yet we agree that such cases do occur. We propose that these cases are distinguished in studies of infantile spasms by being called *infantile spasms single-spasm variant (ISSV).* A child with single spasms and hypsarrhythmia should be classified as *ISSV* rather than *WS*. We do not propose a strict definition of clustering but, as a general guide, a spasm can be regarded as a single spasm if there are no other spasms for one minute beforehand and one minute afterwards.

R4S7: *Classification of children with hypsarrhythmia but no evidence of clinical spasms.* Some children are investigated for symptoms other than clinical spasms and are found to have hypsarrhythmia. If these children, even after video EEG investigation, are found not to have any evidence of clinical spasms, we propose that they are classified as having *hypsarrhythmia without infantile spasms (HWIS).*

R4S8: *Relationship between IS, WS, ISSV and HWIS.* We propose using the term *infantile spasms* as an inclusive term for all children with clinical spasms who have evidence of EEG abnormalities consistent with the clinical syndrome of infantile spasms that has been described in previous studies. The terms *West syndrome* and *infantile spasms single-spasm variant* describe more specific subgroups of infantile spasms. Investigators might wish to report studies of children with all forms of infantile spasms and report the proportions in their study with WS and ISSV. Or they might wish to perform a study that included, say, only children with WS and ISSV with hypsarrhythmia. Studies using developmental and EEG outcomes might wish to include children with HWIS. Consistent use of these definitional terms and a clear statement of how many children came from each group will assist those who wish to use and interpret study data. We believe that these definitions clearly distinguish clinical subgroups, encouraging both clarity and flexibility in study design.

R4S9: *Flow diagrams illustrating the relationships between IS, WS, ISSV and HWIS.* Figures 1 and 2 [not reproduced in this thesis but similar to figures 5.1 and 5.2 on pages 189 and 190] illustrate these relationships. They also illustrate the relationships of these terms to the 5-axis system proposed by the ILAE Task Force on Classification and Terminology, 2001 [233].

R4S10: *Definition of clinical spasms.* We propose that the term *clinical spasms* is used to describe brief and synchronous movements of the head, trunk and limbs, or sometimes of the head, trunk or limbs alone. These movements have a longer duration than the movement of myoclonus, and they are shorter than the movement associated with a tonic seizure. Thus, their duration is approximately one second. The subtlest movement that might be classifiable as a

clinical spasm is a head nod. We prefer the term *clinical spasms* to the term *epileptic spasms* to describe the ictal phenomenology (Axis 1 of the proposed ILAE 5-axis scheme).

R4S11: *Subtle ictal events.* More subtle movements may constitute the clinical attack associated with hypsarrhythmia. Such movements include episodes of gasping and isolated eye movements. We propose that children with these subtle ictal events are classified as having HWIS because such events are more difficult to count and are not suggested by the term spasms. Ideally, a video EEG would be performed to confirm that spasms are indeed not occurring.

R4S12: *Seizure type.* We propose using the term *epileptic spasms* to describe clinical spasms associated with an epileptiform EEG. This corresponds to Axis 2 of the ILAE scheme. This term would include conditions such as the periodic spasms of Gobbi and infantile spasms [25, 29]. The term *epileptic spasms* implies that the EEG is consistent with the diagnosis of an epilepsy, but does not by itself imply hypsarrhythmia or any more specific EEG pattern.

R4S13: *Relationship between clinical spasms, epileptic spasms, and infantile spasms.* Using these definitions and classification, clinical spasms, epileptic spasms, and infantile spasms correspond with axes 1 (ictal phenomenology), 2 (seizure type), and 3 (syndrome) respectively of the ILAE 5-axis scheme.

R4S14: *Syndrome classification of IS.* With respect to Axis 3 (syndrome) of the ILAE proposed diagnostic scheme, we propose that *infantile spasms* is the syndrome of epileptic spasms with onset generally during the first two years of life in association with focal or diffuse interictal EEG abnormalities [25]. We propose that *West syndrome* is defined by the association of infantile spasms, at least some of which occur in clusters, with an interictal EEG showing hypsarrhythmia. This may be either "classical" hypsarrhythmia, or hypsarrhythmia with modified features. *Infantile spasms single-spasm variant* is another form of infantile spasms.

R4S15: *Ictal unit of infantile spasms.* There is disagreement about whether the appropriate ictal unit in studies of infantile spasms should be the spasm or the cluster of spasms. Most participants of West Delphi thought that the more appropriate ictal unit was the cluster of spasms. However, we felt that there was limited value in outcomes that rely on measurement of ictal units, such as time to 50% reduction of spasms or the proportion of study participants having a 50% or greater reduction in spasms.

R4S16: *Definition of hypsarrhythmia.* We propose that the term *hypsarrhythmia* is used to describe an EEG pattern that is characterised by random, high-voltage spikes and slow waves. The most striking features of hypsarrhythmia are: high-voltage (generally $> 200\,\mu V$) slow waves; spikes and waves from many foci and varying with time; a lack of synchrony and a "chaotic" appearance. The typical appearance is more likely to be found in earlier stages of the disorder and when onset occurs at a younger age. The hypsarrhythmic pattern may disappear during REM sleep, but it may be found with greater sensitivity in some other stages of sleep [66].

R4S17: *Modified and atypical hypsarrhythmia.* With respect to the use of the term *modified hypsarrhythmia* [8][67] and its synonym atypical hypsarrhythmia [32], we endorse the recommendation of the 1991 workshop on infantile spasms (Commission on Pediatric Epilepsy of the International League Against Epilepsy 1992 [28]) that study participants with modified hypsarrhythmia are not reported in dichotomised groups but that, where appropriate, a description is given of the individual modifying features. The presence of modified features may depend upon the stage of infantile spasms at which the EEG is performed; it may depend upon treatment; and as an aggregate variable, it probably has little practical prognostic signif-

icance in randomised studies.

R4S18: *Use of electroencephalograms (EEGs) in studies of IS.* We suggest that EEG findings provide essential information in studies of infantile spasms. We recommend a degree of standardisation in the timing of EEG investigations, and that investigators limit potential information bias in studies by making allowance for differences in sensitivity of different investigations. Increased sensitivity is likely in the case of video EEGs, for longer periods of recording, and for recordings that include periods of non-REM sleep. While less sensitive investigations are permitted, it is prudent to design studies that use increasingly more sensitive investigations before inferring that EEG abnormalities are genuinely not present.

R4S19: *Etiologic subgroups of IS.* Several terms have been used to describe etiologic subgroups of IS, but these terms have not been used consistently between studies. There remains incomplete agreement about the use of the terms *symptomatic, idiopathic,* and *cryptogenic* even though they are used in the classification of several epilepsies.

R4S20: *Idiopathic IS.* The term *idiopathic infantile spasms* is used to describe cases in which there are infantile spasms without any identifiable underlying cause, nor other neurologic signs or symptoms. Such cases are sometimes presumed to be genetic in origin - but no proof currently exists to support this statement [233]. A more restricted classification of idiopathic IS has been suggested in which cases are likely to show disappearance of spikes after the administration of intravenous diazepam, and to have hypsarrhythmia between spasms within a single cluster of spasms [233][36][51].

R4S21: *Cryptogenic IS.* The term *cryptogenic infantile spasms* has been used to describe cases suspected of being symptomatic but for whom an underlying structural or biochemical cause could not be identified. It has been suggested that the term *probably symptomatic* is preferred to *cryptogenic* [233].

R4S22: *Symptomatic IS.* The term *symptomatic infantile spasms* has been used to refer to cases in which the seizures result from one or more identifiable structural lesions of the brain, but has also been applied in some studies to children who have developmental arrest or regression that seemed to precede the onset of spasms.

R4S23: *Problems with the terms idiopathic, cryptogenic and symptomatic.* These terms are considered by some investigators to be unsatisfactory. For example, many biochemical defects are genetic, yet cases with proven biochemical defects are likely to be classified as symptomatic cases. Also, the classification of cases as cryptogenic classification is likely to be prone to poor inter-rater reliability. Furthermore, assessing developmental delay at onset and the timing of onset of spasms is difficult.

R4S24: *Predisposed and non-predisposed subgroups.* Since there remains disagreement about use of the terms *symptomatic, idiopathic,* and *cryptogenic,* we recommend the introduction of two new terms. Cases that are shown to have underlying conditions should be referred to as belonging to a *predisposed subgroup.* Those without any identified underlying condition should be referred to as *non-predisposed,* even where it is suspected that there is an unidentified underlying cause. We feel that these new terms are objective and have several advantages. First, the term *symptomatic* is less than ideal since the spasms themselves are a symptom and a sign and, in this sense at least, all cases of infantile spasms are symptomatic. Second, the term *predisposed* does not imply a causal relationship between the underlying condition and the infantile spasms, but rather that the risk of infantile spasms is modified by the associated underlying

condition. Third, this classification makes no global distinctions between structural, biochemical, genetic or other conditions, though permits all predisposed cases to be further classified into subgroups according to their known underlying conditions. Fourth, investigators remain free to use and define the terms *idiopathic, cryptogenic* and *symptomatic* in further studies.

R4S25: *Developmental delay at onset of spasms and etiologic subgroups.* Though developmental delay at the time of onset of infantile spasms has in many previous studies been regarded as indicating a symptomatic underlying condition, it is not possible to know if the epileptic process that causes hypsarrhythmia has preceded the onset of clinical spasms and has alone been responsible for the developmental delay. In other words, developmental delay before onset of spasms does not reliably indicate a predisposing condition. For this reason, we recommend that developmental delay at the time of onset of spasms is reported independently of etiologic subgroups.

R4S26: *Timing the classification of cases into etiologic subgroups.* We propose that studies of infantile spasms distinguish two etiologic classifications: the first at the time of treatment decision, and the second at the time of study completion. A case may enter a randomised study without a diagnosed predisposing condition, but a predisposing condition may be diagnosed later in the study. It is useful to record the frequency of such changes in classification. We recommend that the later classification be used as the "gold standard" for subgroup analyses. However, it is useful to report which conditions are associated with delays in diagnosis, since this information may modify treatment choices.

R4S27: *Classification and reporting of prognostic factors.* We propose that the following baseline characteristics should be reported for each treatment or intervention group: (1) etiologic subgroup; (2) sex; (3) age at onset (median and range, and proportions in each age category); (4) gestation (proportion born preterm, and median gestation); (5) birthweight (median birthweight and proportion under 1500 grams); (6) preceding seizures; (7) concurrent and previous treatment with AEDs or steroids; (8) lead time from apparent onset of spasms to treatment (median and range); (9) presence of hypsarrhythmia. Attention should be drawn to large differences that might bias the results, even where these have occurred by chance.

R4S28: *Developmental delay at onset of spasms as a prognostic factor.* Studies of infantile spasms should report, as a baseline characteristic, the proportion of children in each treatment group who appeared to have developmental delay at the time of onset of spasms. However, it should be appreciated that the exact timing of onset of spasms and of any apparent developmental delay may be difficult to assess, and that there is a high risk of misclassification of this characteristic.

R4S29: *Categories of age at onset of spasms.* Infantile spasms typically have an onset between 3 and 12 months of age. Younger and older children are more likely to have other conditions, and there is a greater risk of misclassification. Also, age at onset of spasms may influence outcomes. We propose that studies of West syndrome and infantile spasms report outcomes for children in the age groups: (1) less than three months of age (corrected for preterm delivery); (2) 3 months (corrected age) and up to 12 months of age; (3) 12 months of age and older. We propose that these be referred to respectively by the terms: *early onset, classic onset,* and *late onset.* Onset would rarely occur after two years of age, but it is biologically implausible to set an absolute upper age limit.

R4S30: *Types of intervention.* We encourage study designs that use randomized interventions,

since these are less prone to selection and classification biases. However, we would also encourage the collection of data from non-randomised studies, since these permit sensitivity analyses and may involve larger numbers. Furthermore, because of larger numbers, they may improve estimates of risks from adverse events.

R4S31: *Duration of treatment.* We propose that treatments for infantile spasms should be considered to have had a sufficient therapeutic trial after 14 days. In general, it is necessary to give a treatment for 14 days before deciding that it has no treatment effect, but withdrawal should be considered sooner if there is an adverse effect of that treatment. We propose that any study that uses a different period of necessary and sufficient therapeutic trial should state a rationale or empirical evidence for that decision.

R4S32: *Cessation of spasms as primary outcome measure for studies of IS.* We propose that the primary outcome of studies of infantile spasms is *cessation of spasms*, and we suggest a standard definition for this outcome. Without qualification, the term *cessation of spasms* should denote that no clinical spasms have been witnessed from a time within 14 days of treatment, and for a period of at least 28 consecutive days from the time of the last witnessed spasm. Studies of infantile spasms should report the number and proportion of children in each treatment group who meet these criteria.

R4S33: *Essential EEG outcome measures.* Although we have not determined, in terms of prognosis for development and function, the clinical importance of cessation of spasms and resolution of abnormal EEG findings, we feel that it is essential to report the EEG status of children at baseline and at follow-up. We suggest that an EEG is performed at least: (1) before treatment is allocated; (2) between study days 14 and 21 (that is, within 7 days of the end of the period of sufficient therapeutic trial); and (3) between study days 42 and 49 (that is, after the period during which there should have been 28 days of freedom from spasms). If less sensitive investigations do not show hypsarrhythmia, we recommend that a video EEG is performed to strengthen the inference that the hypsarrhythmia has resolved. Although it might be inferred that the EEG remains abnormal in cases where there are continuing spasms, it is useful to have information from EEGs even in children with continuing spasms. We regard this information as essential because it will help to inform us about the prognostic importance of EEG findings, and about treatment effects on the EEG.

R4S34: *Essential adverse effect outcome measures.* Studies should report all deaths occurring during the study period, even when they are not regarded as attributable to treatment. Study reports should state which adverse events were investigated, how they were sought, and how they were classified.

R4S35: *Other important outcome measures.* We propose that at least the following outcomes and measures be reported, by intervention group, in studies of infantile spasms: (a) Cessation of spasms [number and proportion with last witnessed spasm before the end of day 14 of treatment and with no spasms for 28 consecutive days thereafter]; (b) Development at 2 years of age [median and ranges for tests chosen]; (c) Deaths and other serious adverse events [numbers and descriptions of events]; (d) Relapse [numbers and proportion of primary responders relapsing; proportion of whole intervention group relapsing (that is, including non-responders); and distributions of time to relapse (from time of response)]; (e) Presence of and progression to other seizure types [numbers, proportions, and seizure types]; (f) Non-serious adverse events [numbers, proportions, and description of events]; (g) Resolution of hypsarrhythmia at a time between days 14 and 21, and between days 42 and 49 of the study [numbers with hypsar-

rhythmia at start of study, at study day 14 and at study day 42; proportions, and types of EEG performed].

R4S36: *Time to cessation of spasms.* Time to cessation of spasms can be represented by actuarial curves and is a clinically useful outcome that might inform future study designs. We propose that it is permissible for studies to report, in addition to "time to 28-days of spasm-freedom", "time to last witnessed spasm in cases that were primary responders." This gives a useful and intuitive clinical measure that can be examined using the statistical techniques of survival analysis. Measures of time to cessation of spasms are more reliable and informative than measures of time to 50% reduction in ictal units.

R4S37: *Relapse.* The following should be considered to constitute a relapse of infantile spasms at any stage after a primary response has been obtained: 1) any episode of spasms occurring in clusters; and 2) two or more episodes of spasms that occur singly but not in clusters. A single witnessed spasm would not be reliable and should not be classified as a relapse. Because primary response is defined by cessation of spasms, persistent or recurrent hypsarrhythmia should not be considered to be a relapse unless it is accompanied by witnessed spasms. However, the persistence or recurrence of hypsarrhythmia should be reported as part of a secondary and essential outcome measure.

R4S38: *Pyridoxine-dependent seizures.* Pyridoxine dependent seizures are rare. They even more rarely have the clinical manifestation of infantile spasms, though this is thought to be most likely when other seizure types have occurred before the onset of spasms. Giving intravenous pyridoxine is associated with a risk of apnea. It requires close monitoring, and is not known to be associated with rapid resolution of hypsarrhythmia. Oral pyridoxine seems to be associated with a median time to response of several days. Thus, incorporating a diagnostic and therapeutic test of pyridoxine into study designs is challenging.

R4S39: *Pyridoxine-responsive seizures.* The Cochrane review did not identify any RCT evidence of treatment effect for pyridoxine in infantile spasms, but some investigators use pyridoxine as an initial or adjunct treatment of infantile spasms. If pyridoxine is used, the report should clearly state its timing, dose, and duration.

R4S40: *Aggregation of data from several or many studies.* Incorporating data from many and larger studies is a longer-term goal of doctors who are interested in making the best treatment decisions for children with infantile spasms. For randomised controlled trials, there is a Cochrane review of treatments for infantile spasms. This will continue to provide meta-analyses of randomised studies of infantile spasms. For studies with randomised and other designs, we recommend the use of uniform definitions and classification that will facilitate aggregation of data that avoids ambiguity, confusion or misclassification.

R4S41: *Areas for future consensus.* There remain areas of incomplete consensus, such as how we might aggregate data from studies that do not meet the inclusion criteria of the Cochrane review of treatments for infantile spasms. In the future, we might wish to develop a more detailed structure for reporting of adverse events, and recommendations on which tools to use to assess developmental outcomes and to classify disability. Finally, we found it difficult to provide a detailed description of the limits of definition of hypsarrhythmia, and a future consensus might wish to revisit this issue.

R4S42: *Summary of West Delphi consensus statement.* This consensus is the result of many hours of consideration by the X participants. We aimed to produce proposals that will assist investi-

gators in designing studies but which are not unnecessarily constraining. We have attempted to clarify old terms and have generally avoided new terms. The main proposals that might be considered to be new concepts are: (1) definitions of the terms clinical spasms, epileptic spasms, and infantile spasms that conform to the 5-axis ILAE proposal; (2) syndrome classification for IS, WS, ISSV, and HWIS; (3) classification by age at onset into early onset, classic onset and late onset groups; (4) the proposal for an etiologic classification into groups described as *predisposed* and *non-predisposed*; and (5) standardised definitions of response and relapse.

Appendix D

West Delphi Consensus Statement

This appendix contains the West Delphi consensus statement as published in *Epilepsia* 2004;45:1416-28 [209]. The contributing authors, members of the West Delphi Group, are listed in appendix A.4 on page 243.

West Delphi Proposal

1. *Introduction to West Delphi.* The West Delphi Proposal is a consensus statement that proposes a series of definitions and standards for use in studies of infantile spasms. In particular, it aims to provide clearer definitions of cases and etiologic subgroups, and a standard for outcomes and outcome measures. We hope that this will help those who wish to design future studies of infantile spasms, and that such studies will provide optimal information for those who wish to learn from these studies and to choose the best approach to treating infantile spasms.

Case definitions

2. *Infantile spasms.* We propose using the term *infantile spasms (ISs)* to describe an epilepsy syndrome that rarely has onset in children over two years old and usually has onset in children aged less than one year. Its main clinical manifestation is *clinical spasms* that usually occur in clusters. There are many potential etiologies or associated conditions. The most characteristic EEG finding is hypsarrhythmia. However, hypsarrhythmia is not found in all cases, nor is it found throughout the clinical course of the condition. Hypsarrhythmia is usually interrupted during a clinical attack of epileptic spasms. The spasms are often associated with developmental arrest or regression.

3. *West syndrome.* We propose using the term *West syndrome (WS)* to describe the combination of spasms that occur in clusters and hypsarrhythmia on an EEG. We do not require, as have some previous definitions of West syndrome, that there is evi-

dence of delayed development before the onset of spasms. Some participants wished to classify children with single spasms (that is, without spasms in clusters) and with hypsarrhythmia as having *West syndrome,* but most preferred to reserve the term West syndrome for cases with clustered spasms.

4. *Significance of developmental delay.* We see no reason for including developmental delay at the time of onset as a defining feature of West syndrome. Indeed, developmental delay at onset of spasms is likely to be assessed unreliably because spasms are often subtle and their true time of onset is often unrecognised, and also because development is hard to assess in early infancy. However, we feel that information about unequivocally normal development at the time of onset of spasms is worth recording, since this may be associated with better developmental outcome. Apparently abnormal development may be confounded by the effect of unrecognised spasms at onset or the epileptic encephalopathy.

5. *Infantile spasms – single-spasm variant.* It is less usual for infantile spasms to always occur singly rather than in clusters, yet we agree that such cases do occur. We propose that these cases are distinguished in studies of infantile spasms by being called *infantile spasms single-spasm variant (ISSV).* A child with single spasms and hypsarrhythmia should be classified as ISSV rather than WS. We do not propose a strict definition of *clustering* but, as a general guide and until further evidence is available, we suggest that a spasm can be regarded as a single spasm if there are no other spasms for one minute beforehand and for one minute afterwards. Any definition of clustering should be clearly stated. We wish to emphasise that a child with single spasms and without hypsarrhythmia is rare and such cases are likely to have a diagnosis other than ISSV. Some participants felt that they would never diagnose infantile spasms in such a case. We would suggest that authors state clearly, in cases with neither clustering of spasms nor hypsarrhythmia, why they are accepting the diagnosis of ISSV.

6. *Hypsarrhythmia without infantile spasms.* Some children are investigated for symptoms other than clinical spasms and are found to have hypsarrhythmia. If these children, even after video EEG investigation, are found not to have any evidence of clinical spasms, we propose that they are classified as having *hypsarrhythmia without infantile spasms (HWIS).* Future studies will inform us whether these children have a high risk of developing infantile spasms at a later date, and about their developmental outcome.

7. *Relationship between definitional terms.* We propose using infantile spasms as an inclusive term for all children with clinical spasms who have evidence of EEG abnormalities consistent with the clinical syndrome of infantile spasms - typically, though not necessarily, hypsarrhythmia or modified hypsarrhythmia (see statements 16 and 17) - provided that the EEG findings do not suggest another specific diagnosis. The terms *West syndrome* and *infantile spasms single-spasm variant* describe specific subgroups of infantile spasms. Investigators might wish to report studies of children with all forms

of infantile spasms and report the proportions in their study with *WS* and *ISSV*. Or they might wish to perform a study that included, say, only children with *WS* and *ISSV with hypsarrhythmia*. Studies that focus on developmental and EEG outcomes might wish to include children with *HWIS* (though *HWIS* is not a subgroup of *ISs*). Consistent use of these definitional terms and a clear statement of how many children came from each group will assist those who wish to use and interpret study data. We believe that these definitions clearly distinguish clinical subgroups, encourage clarity, and permit flexibility in study design.

8. Our proposed relationships between IS, WS, ISSV and HWIS are illustrated in [figures D.1 and D.2]. These figures also illustrate the relationships between these terms and the 5-axis system proposed by the ILAE Task Force on Classification and Terminology, 2001 [233].

9. *Features of clinical spasms*. We propose that the term *clinical spasms* is used to describe brief and synchronous movements of the head, trunk and limbs, or sometimes of the head, trunk or limbs alone. The movements may be flexor or extensor, or a mixture of extensor and flexor movements, and they may be asymmetric. These movements have a longer duration than the movement of myoclonus, and they are shorter than the movement associated with a tonic seizure. Thus, their duration is approximately one second. The subtlest movement that might be classifiable as a clinical spasm is a head nod. Though it has been suggested that the term describing this seizure semiology should be *epileptic spasm* (ILAE Glossary of Descriptive Terminology for Ictal Semiology, 2001: paragraph II 1.1.1.1), we propose using the term *clinical spasms* to describe the ictal phenomenology, and reserving the term *epileptic spasms* to describe the seizure type [234].

10. *Subtle spasms*. More subtle movements, often described as *subtle spasms*, may constitute the clinical attack associated with hypsarrhythmia. Such movements include episodes of yawning, gasping, facial grimacing, isolated eye movements, and transient focal motor activity. These cases may be having focal seizures, and the episodes are difficult to count and record. Ideally, a video EEG would be performed to confirm that clinical spasms are not occurring.

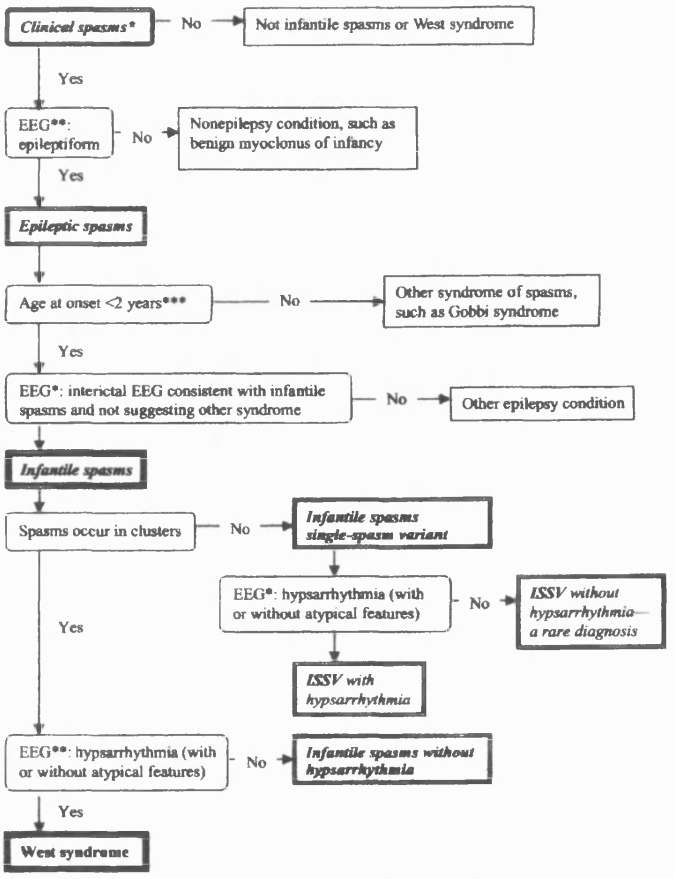

FIG. 1. Classification of infantile spasms for study inclusion.

*Excludes subtle spasms.

**EEG, standard, sleep and video EEGs are performed, as necessary, before excluding a positive finding.

***2 years is not an absolute upper limit, but substantially older cases would be likely to be classified as another syndrome, such as that of periodic spasms. If thought to be infantile spasms, they would be clearly identified as unusual, and the numbers of such patients should be clearly stated.

Suggested cross-reference to ILAE multiaxial classification:

Axis 1 (ictal phenomenology): ***clinical spasms***

Axis 2 (seizure type): ***epileptic spasms***

Axis 3 (syndrome): ***infantile spasms (ISs), West syndrome (WS), and infantile spasms single-spasm variant (ISSV) are syndrome subgroups of ISs.***

Suggested use for terms:

- Studies of *infantile spasms* would include cases of ISSV and cases of West syndrome, unless exclusions or restrictions are explicitly stated
- Studies of *West syndrome* would exclude cases without clustered spasms and cases without hypsarrhythmia

Note that this classification requires clusters of spasms for a diagnosis of West syndrome. Cases with spasms occurring singly and without any witnessed clusters, even when associated with hypsarrhythmia, are not classified as West syndrome.

Figure D.1: Classification of infantile spasms for study inclusion as it appears in the West Delphi consensus statement.

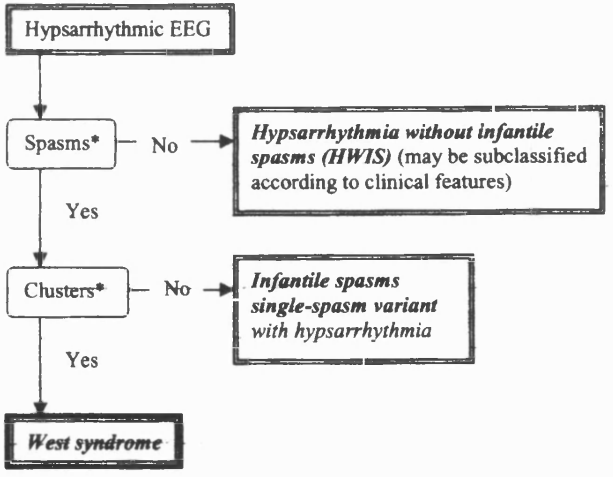

FIG. 2. Classification of children with hypsarrhythmia without clinical spasms but who may have subtle spasms. It is well known that hypsarrhythmia can occur in the absence of spasms and sometimes without any evident clinical seizure (26). Because hypsarrhythmia is effectively the presenting feature in such cases (at least, with respect to considering a diagnosis of infantile spasms), it is useful to have a scheme for classification, conditional on the presence of hypsarrhythmia.
This flow diagram suggests a classification for children with hypsarrhythmia identified at younger than 2 years.

*If spasms or clusters are not observed clinically, we recommend performing video-EEG for a period of ≥24 h to rule out their occurrence reliably.

Figure D.2: Classification of children with hypsarrhythmia without infantile spasms as it appears in the West Delphi consensus statement.

11. *Subtle spasms at onset or at follow up.* We propose that children with these subtle ictal events are classified at onset as having *hypsarrhythmia without infantile spasms (HWIS)* because the events are different from clinical spasms, they are difficult to recognise and count, and they are not reliably measured as a primary clinical outcome. However, we suggest that investigators should, during follow up of a case of infantile spasms, report subtle movements associated with typical electrodecremental EEG changes or interruption in the interictal background, and that this combination of clinical and neurophysiological findings would be sufficient to constitute electroclinical non-response or relapse.

12. *Epileptic spasms.* We propose using the term *epileptic spasms* to describe the epileptic seizure type of clinical spasms associated with an epileptiform EEG. This corresponds to Axis 2 of the proposed ILAE scheme. This term would include conditions such as the periodic spasms of Gobbi and infantile spasms [25, 29]. The term *epileptic spasms* implies that the EEG is consistent with the diagnosis of an epilepsy, but does not by itself imply hypsarrhythmia or any more specific EEG pattern.

13. *Relationship to proposed ILAE 5-axis system.* Using these definitions and classification, clinical spasms, epileptic spasms, and infantile spasms correspond with axes 1 (ictal phenomenology), 2 (seizure type), and 3 (syndrome) respectively of the proposed ILAE 5-axis scheme. West syndrome is a syndrome in its own right and a subgroup of infantile spasms, as is ISSV.

14. With respect to Axis 3 (syndrome) of the proposed ILAE diagnostic scheme, we propose that infantile spasms is the syndrome of epileptic spasms with onset generally during the first two years of life, in association with high voltage, multifocal or diffuse interictal EEG abnormalities [25]. We propose that West syndrome is defined by the association of clinical spasms, at least some of which occur in clusters, with an interictal EEG showing hypsarrhythmia. This may be either "classic" hypsarrhythmia, or hypsarrhythmia with modified features. *Infantile spasms single-spasm variant* is another form of infantile spasms and is also regarded as an epilepsy syndrome.

15. *Ictal unit of infantile spasms.* There is disagreement about whether the appropriate ictal unit in studies of infantile spasms should be the spasm or the cluster of spasms. Most West Delphi participants thought that the more appropriate ictal unit was the cluster of spasms. However, we felt there was limited value in outcomes that rely on measurement of ictal units, such as time to 50% reduction of spasms or the proportion of study participants having a 50% or greater reduction in spasms.

Electrographic features

16. *Hypsarrhythmia.* We propose that the term *hypsarrhythmia* is used to describe an EEG pattern that is characterised by random, high-voltage spikes and slow waves. The most striking features of hypsarrhythmia are: high-voltage (generally >200 microvolts) slow waves with variable amplitude; spikes and waves from many foci and varying with time; and a lack of synchrony with a generally "chaotic" appearance. The typical appearance is more likely to be found in earlier stages of infantile spasms and when onset occurs at a younger age. The hypsarrhythmic pattern may disappear during REM sleep, but it may be found with greater sensitivity in some other stages of sleep [66].

17. *Modified and atypical hypsarrhythmia.* With respect to the use of the term *modified hypsarrhythmia* [8, 67] and its synonym (or at least near-synonym) *atypical hypsarrhythmia* [32], we endorse the recommendation of the 1991 workshop on infantile spasms [28] that study participants with modified hypsarrhythmia are not reported in dichotomised groups but that, where appropriate, a description is given of the individual modifying features. The presence of modified features may depend upon the stage of infantile spasms at which the EEG is performed; it may depend upon treatment; and as an aggregate variable, it probably has little practical prognostic significance in randomized studies.

18. *Forms of EEG recording.* EEG findings provide essential information in studies of infantile spasms. We recommend a degree of standardisation in the timing of EEG investigations, and that investigators limit potential information bias in studies by making allowance for differences in the sensitivity of different investigations. Increased sensitivity is likely in the case of video EEGs, with longer periods of recording, and with recordings that include periods of non-REM sleep. While performing less sensitive investigations is reasonable, it is prudent to design studies that use more sensitive investigations before inferring that EEG abnormalities are genuinely not present.

Etiology of infantile spasms

19. *Etiologic subgroups of infantile spasms.* Several terms have been used to describe etiologic subgroups of ISs, but these terms have not been used consistently between studies. There remains incomplete agreement about the use of the terms *symptomatic, idiopathic,* and *cryptogenic* even though such terms are also used in the classification of other epilepsies. The terms idiopathic and cryptogenic have been used in some studies as synonyms of each other and as antonyms of symptomatic.

20. *Idiopathic infantile spasms.* The term *idiopathic infantile spasms* is used to describe cases in which there are infantile spasms without any identifiable underlying cause, nor other neurologic signs or symptoms. Such cases may be associated with a family history. While we agree that cases in this group may have good developmental out-

comes, we do not approve making eventual normal development part of its definition, since we are reserving its use as part of an etiologic classification for use at the time of study enrolment.

21. *Cryptogenic infantile spasms.* The term *cryptogenic infantile spasms* has been used to describe cases suspected of being symptomatic but for whom an underlying structural or biochemical cause could not be identified. Features suggesting an unidentified underlying cause include preceding developmental delay, or other neurologic features, such as seizures. It has been suggested that the term *probably symptomatic* is preferred to *cryptogenic* [233], though West Delphi participants had a range of views on this. Some prefer to retain the term *cryptogenic*; some prefer *probably symptomatic*; and some suggest that, if we cannot identify the underlying cause, we ought to use the term *non-symptomatic* rather than subjectively classify cases further.

22. *Symptomatic infantile spasms.* The term *symptomatic infantile spasms* has been used to refer to cases in which the seizures result from an identifiable cause, and often to refer also to cases in which neurological features or an unequivocal developmental delay precede the onset of spasms. We suggest reserving the term *symptomatic* for cases with an identified underlying disorder, and classifying cases with neurological symptoms, signs or developmental delay, but no proven cause or etiology, as *cryptogenic*.

23. *Specific etiologies.* However constituted, the etiologic subgroups discussed above will include children with different underlying causes, which may or may not be identified, and such aggregation into etiologic subgroups is of limited value. However, within any one study, it is only possible to obtain precise estimates of effect, and to perform formal statistical tests for heterogeneity of effect, on groups with specific diagnoses if they are relatively commonly associated with infantile spasms. An example of such commonly associated diagnoses is tuberous sclerosis. Greater homogeneity of study design will help in aggregating data about rare causes of infantile spasms.

24. *Timing of etiologic classification.* It is often unclear in study reports whether the classification into etiologic subgroups is based on diagnostic information known at the time of treatment decision or randomization, or information available at the time of study completion. If the data are to be used to inform future treatment choice, it is rational for the study to report outcomes according the classification made at the time of treatment decision. This avoids the information bias introduced by reclassification of cases between time of treatment decision and study completion. Initial classification is the natural choice for stratified analyses by intention-to-treat.

25. We ought also to use the more complete and specific diagnostic information that is available at the time of study completion. This informs us about outcomes and treatment choice for children with specific diagnoses, though we should be aware of the bias that might be introduced by incomplete diagnostic information at the time

of treatment decision. We propose that, in order to make this clear, studies reserve the terms *cryptogenic, idiopathic,* and *symptomatic* to refer to an etiologic classification made at the time of randomisation or treatment choice, and that they report the final *diagnostic classification* in more specific diagnostic groups. We suggest a list of specific diagnostic groups in Appendix B. Of course, study inclusion criteria or stratified randomisation might include more specific diagnostic groups, such as tuberous sclerosis, but the study report should make clear if there has been diagnostic reclassification of cases by the time of study completion.

Reporting baseline characteristics in studies of infantile spasms

26. *Baseline characteristics in interventional studies.* We propose that the following baseline characteristics should be reported for each treatment or intervention group: (a) etiologic group, if used for pre-randomisation stratification; (b) sex; (c) age at onset (median and range, and proportions in each age category – see statement 27); (d) gestation (proportion born preterm, and median gestation); (e) birthweight (median birthweight and proportion under 1500 grams); (f) preceding seizures; (g) concurrent and previous treatment with AEDs or steroids; (h) lead time from apparent onset of spasms to treatment (median and range); (i) presence of hypsarrhythmia; and (j) unequivocally normal development at apparent onset of spasms. Attention should be drawn to large differences that might bias the results, even where treatments have been allocated randomly and these differences must have occurred by chance.

27. *Classification by age at onset of spasms.* Infantile spasms typically have an onset between 3 and 12 months of age. Younger and older children are more likely to have other conditions, and there is a greater risk of misclassification. Also, age at onset of spasms may influence outcomes. We propose that studies of infantile spasms report outcomes for children in age of onset groups: (1) less than three months of age (corrected for preterm delivery); (2) 3 months (corrected age) and up to 12 months of age; (3) 12 months of age and older. We propose that these be referred to respectively by the terms: *early onset, classic onset,* and *late onset.* Onset would rarely occur after two years of age, but it is biologically implausible to set an absolute upper age limit.

Duration of treatment

28. *Duration of treatment in interventional studies.* We propose that treatments for infantile spasms should be considered to have had a sufficient therapeutic trial after 14 days. In general, it is necessary to give a treatment for 14 days before deciding that it has no treatment effect, but withdrawal should be considered sooner if there is an adverse effect of that treatment. We suggest that any study that uses a different period of necessary and sufficient therapeutic trial should state a rationale or empirical evidence for that decision. If adjunct treatments are used, the study protocol should state clearly how these might affect outcome.

Outcomes

29. *Primary clinical outcome.* We propose that the *primary clinical outcome* of studies of infantile spasms is *cessation of spasms*, and we suggest a standard definition for this outcome. Without qualification, the term *cessation of spasms* should denote that no clinical spasms have been witnessed from a time commencing within 14 days of treatment, and for a period of ≥ 28 consecutive days from the time of the last witnessed spasm. Studies of infantile spasms should report the number and proportion of children in each treatment group who meet these criteria.

30. *Timing of EEG investigations.* Although we do not have evidence for the clinical importance of cessation of spasms and resolution of abnormal EEG findings, in terms of prognosis for development and function, we propose that it is essential to report the EEG status of children at baseline and at follow-up. We suggest that an EEG is performed at least:

- before treatment is allocated;
- between study days 14 and 21 (that is, within 7 days of the end of the period of sufficient therapeutic trial); and
- between study days 42 and 49 (that is, after the period during which there should have been 28 days of freedom from spasms).

31. *EEG classification.* Resolution of hypsarrhythmia is a more appropriate EEG outcome than normalization of EEG, since with many underlying etiologies we cannot expect the background EEG to normalize even if epileptiform changes resolve. Also, there may be progression to other seizure types without any evidence of infantile spasms or hypsarrhythmia.

Electroclinical outcomes

32. If less sensitive investigations do not show hypsarrhythmia, we recommend that a sleep EEG is performed to provide stronger evidence that the hypsarrhythmia has resolved. Ideally, there would be a video EEG recording that includes sleep. There is no evidence for recommending a specific duration for video EEG recording, but a 24-hour period is typical and some participants thought 6 hours would be as sensitive as 24 hours. Although it might be inferred that the EEG remains abnormal in cases where there are continuing spasms, it is also useful to have information from EEGs in children with continuing spasms. We regard this information as essential because it will help to inform us that the seizure type has not changed, about the prognostic importance of EEG findings, and also about treatment effects on the EEG.

33. *Primary electroclinical response.* Some West Delphi participants are uneasy with the idea that children with no witnessed spasms but continuing hypsarrhythmia should

be classified as primary responders. They suggest that a primary responder should have both cessation of spasms and resolution of hypsarrhythmia. We propose the term *primary electroclinical outcome* to describe this combination of outcomes, and we propose that it be regarded as an essential outcome [182].

34. Studies that report both *primary clinical outcome* and *primary electroclinical outcome* provide important information about how often the clinical response is associated with resolution of hypsarrhythmia. Such studies would permit a degree of extrapolation of data from studies performed in places where access to neurophysiological equipment is more restricted and where the primary electroclinical outcome cannot be reliably determined.

Adverse events

35. *Deaths during study period.* Studies should report all deaths occurring during the study period, even when they are not regarded as attributable to treatment. Study reports should state which adverse events were investigated, how they were sought, and how they were classified.

Outcome measures and analysis of data

36. *Outcome measures.* We propose that at least the following outcomes and measures, stratified by intervention group, are reported in studies of infantile spasms:

- primary clinical response
- primary electroclinical response
- relapse-free primary responses (clinical and electroclinical, numbers and proportions)
- continuing subtle spasms where clinical spasms have ceased
- distribution of time to relapse (from time of randomisation, perhaps best represented graphically as a variable proportion with relapse-free remission over time)
- development at 2 years of age (medians and ranges for tests chosen)
- deaths and other serious adverse events (numbers and descriptions of events)
- presence of and progression to other seizure types (numbers, proportions, and seizure types)
- non-serious adverse events (numbers, proportions, and description of events)

37. *Analyzing different etiologic subgroups.* We suggest that most outcomes are influenced more strongly by underlying disorders than by treatment. We recommend that

investigators exercise caution in performing multiple tests on such outcomes and attributing significant differences to treatments since, in addition to there being biases introduced by multiple testing, the conclusions may lack biological plausibility. However, one aim of treatment is to improve development and function by limiting any damage that might be caused by repeated spasms.

38. *Analyzing time to cessation of spasms.* Time to cessation of spasms can be represented by actuarial curves and is a clinically useful outcome that might inform future study designs. We suggest the convention of reporting time to *28-days of spasm-freedom* for the primary clinical response. This is a useful and intuitive clinical measure that can be examined using the statistical techniques of survival analysis. Measures of time to cessation of spasms are more reliable and informative than measures of time to 50% reduction in ictal units. The primary electroclinical response does not lend itself so readily to such analyses because EEGs are performed in a cross-sectional fashion, whereas clinical observation is a more continuous measure.

39. *Relapse.* The following should be considered to constitute a clinical relapse of infantile spasms at any stage after a primary clinical response has been obtained: (1) any episode of spasms occurring in clusters; (2) two or more episodes of spasms that occur singly but not in clusters; and (3) subtle spasms (if accompanied by an EEG showing appropriate changes). A single witnessed spasm would not be reliable and should not be classified as a relapse of clinical spasms, but investigators might wish to report their occurrence.

Role of pyridoxine (vitamin B6)

40. *Diagnostic role of pyridoxine.* Pyridoxine-dependent seizures are rare [122]. They even more rarely have the clinical manifestation of infantile spasms, though this is thought to be most likely when other seizure types have occurred before the onset of spasms. Giving intravenous pyridoxine is associated with a risk of apnea. It requires close monitoring, and is not known to be associated with rapid resolution of hypsarrhythmia. Oral pyridoxine seems to be associated with a median time to response of several days. Thus, incorporating a diagnostic and therapeutic test of pyridoxine into study designs is challenging.

41. *Treatment role of pyridoxine.* In addition to use in diagnosing potential pyridoxine-dependent seizures, pyridoxine has been used more broadly as a treatment or adjunct treatment for infantile spasms. The Cochrane Review of treatment of infantile spasms did not identify any evidence of treatment effect in trials meeting its inclusion criteria [214, 215]. If pyridoxine is used, the report should clearly state its timing, dose, and duration; and also whether it is being used to exclude a diagnosis of pyridoxine-dependent seizures or as a treatment intervention for infantile spasms in its own right.

Areas of incomplete consensus

42. There remain areas of incomplete consensus. In the future, we might wish to develop a more detailed structure for reporting adverse events, and recommendations on which tools to use to assess developmental outcomes and to classify disability. Finally, we found it difficult to provide a detailed description of the limits of definition of hypsarrhythmia: those designing studies will need to consider the advantages of using several EEG assessors, and how to assess intra-rater and inter-rater agreement in classification of EEGs.

Appendix A of West Delphi consensus statement: List of EEG features that are regarded as *modifying* features of hypsarrhythmia

Asymmetry
Consistent focal discharge
Episodes of voltage attenuatiojn (local, regional, or general)
Excessive rapidity
Excessive slowing
Fragmentation
Increased interhemispheric synchronization
Increased periodicity
Predominant high-voltage, bilaterally asynchronous slow activity

Appendix E

Abbreviations used in this thesis

AAN	American Academy of Neurology
ABC	(Vineland) Adaptive Behavior Composite (score)
ABPI	Association of British Pharmaceutical Industries
ACTH	Adrenocorticotropic hormone (adrenocorticotropin)
ADI	Autism Diagnostic Inventory
ADR	Adverse drug reaction
ADROIT	Adverse Drug Reaction On-line Information Tracking
AE	Adverse event
AED	Anti-epileptic drug
ANOVA	Analysis of variance
BACCH	British Association of Community Child Health
BAN	British Approved Name
BMEI	Benign Myoclonus of Early Infancy
BURP	Bath Unit for Research in Paediatrics
CI	Confidence interval
CNS	Child Neurology Society
CPMP	Committee for Proprietary Medicinal Products
CTX	Clinical Trial Certificate
DDX	Doctors' and Dentists' Exemption Certificate
DISCO	Diagnostic Interview for Social and Communication Disorders
DMEC	Data monitoring and ethics committee
EEG	Electroencephalogram
EIEE	Early infantile epileptic encephalopathy
EME	Early myoclonic encephalopathy
EMG	Electromyogram
HIE	Hypoxic-ischaemic encephalopathy
ICH	International Conference on Harmonisation

ILAE	International League Against Epilepsy
IM	Intramuscular or intramuscularly
ISs or IS	Infantile spasms
ISSV	Infantile spasms, single spasm variant
IU	International Units
LREC	Local research ethics committee
MCA	Medicines Control Agency (Now MHRA)
MedDRA	Medical Dictionary for Regulatory Activities
MEDDRA	Medical Dictionary for Drug Regulatory Affairs
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
MRC	Medical Research Council
MREC	Multicentre research ethics committee
NHS	National Health Service
NHSLA	National Health Service Litigation Authority
nv-CJD	New variant Creutzfeld-Jakob Disease
PSUR	Periodic Safety Update Report
PVH	Periventricular haemorrhage
PVL	Periventricular leukomalacia
REM	Rapid eye movement (sleep stage)
rINN	Recommended International Non-proprietary Name
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
TRH	Thyrotropin-releasing hormone
TSC	Tuberous sclerosis (+/- complex)
UKISS	The United Kingdom Infantile Spasms Study
V-AVFL	Vigabatrin-associated visual field loss
VFL	Visual field loss
WHO	World Health Organisation
WISC	Wechsler Intelligence Scale for Children
WISC-R	Revised Wechsler Intelligence Scale for Children
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WS	West syndrome

Appendix F

Publications Associated with this Thesis

F.1 Original articles

Lux AL, Edwards SW, Osborne JP. Responses of local research ethics committees to a study with approval from a multicentre research ethics committee. *BMJ* 2000;**320**:1182-3.

Osborne JP, Lux AL. Towards an international consensus on definitions and standardized outcome measures for therapeutic trials (and epidemiological studies) in West syndrome. *Brain Dev* 2001;**23**:677-82.

Lux AL, Edwards SW, Hancock E, O'Callaghan, FJK, Johnson AL, Kennedy CR, Newton RW, Verity CM, Osborne JP. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *Lancet* 2004;**364**:1773-78.

Lux AL and Osborne JP for the West Delphi Group. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi Group. *Epilepsia* 2004;**45**:1416-28.

Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, O'Callaghan FJK, Verity CM, Osborne JP. The United Kingdom Infantile Spasms Study, a multicentre randomised trial comparing vigabatrin and hormonal treatment: developmental and epilepsy outcomes to age 14 months. *Lancet Neurol* 2005;**4**:712–7.

F.2 Review articles

Lux AL. West & Son: the origins of West syndrome. *Brain Dev* 2001;**23**:443-6.

Lux AL, Osborne JP. The influence of etiology upon ictal semiology, treatment decisions and long-term outcomes in infantile spasms and West syndrome. *Epilepsy Res* [In press].

F.3 Letters

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F.4 Abstracts of posters and presentations

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Lux AL. Deciding how to treat West syndrome: Ways to use data from the United Kingdom Infantile Spasm Study. Keynote Lecture at the 45th Meeting of the Japanese Society of Child Neurology. ACROS Center, Fukuoka, Japan: 23 May, 2003. *No To Hattatsu* 2003;**35(Suppl.)**:S154.

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